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THE NATURE OF THE PHYSICAL SIGNS OF BUNDLE-BRANCH BLOCK.*

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Bundle-branch, or intraventricular, block is not an uncommon disorder of conduction in the heart. In a previous communication[9] it has been reported as occurring in 9 of 100 unselected cases of cardiac disease, in all of which electrocardiograms were made. During the past 4 years it has been possible for one of us to see 50 cases of this condition in hospitals and practice. Moreover, bundle-branch block is doubtless frequently overlooked since in the absence of an arrhythmia there is often little to direct attention to its presence or to suggest the desirability of obtaining electrocardiograms.

With our present knowledge of the mechanism of auricular fibrillation, of extrasystoles, and of auriculoventricular block, it is possible, in the majority of instances, to recognize these disorders at the bedside. The recognition of bundle-branch block without the aid of galvanometric records would, in like manner, be a distinct advantage. Under such circumstances the clinician would be freed from the necessity of using the electrocardiograph in disorders of the cardiac mechanism save to verify his clinical diagnosis or to

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recognize certain rare abnormalities. In this paper an attempt is made to point out and to illustrate the phenomena by means of which, in the majority of cases, bundle-branch block may be recognized at the bedside.

During the course of observations on the exposed dog's heart, in which a branch of the His bundle had been cut, Eppinger and Rothberger[4] and later, Smith[13] noted that asynchronous contraction of the ventricles could be made out immediately after the experimental section: apparently, such an observation served to inform the workers that the operation had been performed successfully. The only previous attempts to demonstrate by mechanical methods that this phenomenon may be projected to the precordium were made, so far as we are aware, by Kauf[8] and by Eppinger and Stoerk.[5] In each of these contributions a spiked apex ventricular wave was shown to occur on the apex cardiograms from an individual with bundle-branch block. Reduplication of the apex impulse was felt by Eppinger and Stoerk[5] and by Kauf[8] in patients known to have this lesion. However, prior to the report by one of us,[9] no one seems to have noted that this evidence of bundle block might be perceived in most cases by careful examination of the precordium and thus permit of a strictly clinical diagnosis. Additional points of value in the recognition of this condition were noted at that time and are here reëmphasized.

Physical Signs. Examination of the precordium by the usual methods of physical diagnosis has shown the signs of bundle-branch block to be as follows:

TABLE 1.—PHYSICAL SIGNS OF 50 CASES OF BUNDLE-BRANCH BLOCK.

	No.	Per cent.
Visible apical reduplication	42	84
Palpable apical reduplication	40	80
Auscultation:		
Reduplication of first sound at apex	28	56
Asynchronous systolic murmurs	6	12
Single first sound and separated systolic murmur	8	16

The character of the physical signs and the frequency of their evidence in this series are very similar to those noted in the more limited report by King.[9] We are, therefore, surprised that Hill[7] who recently reported a series of 41 cases of bundle-branch block states that such signs are not found with any degree of constancy and that the diagnosis is not possible at the bedside. The auscultatory signs reported by Hill are very similar to those herewith described though they were encountered less frequently in his series: he found visible and palpable reduplication, however, in only 1 of a "few" cases in which special search was made for all the physical signs. No mention is made of the number of cases of the total series observed personally by Hill. In our experience, the visible and palpable reduplication of the apex thrust, and particu-

larly the combination of the two by inspection of the palpating fingers, are more constant (see Table 1) and more characteristic, and therefore more helpful in the diagnosis, than are the auscultatory findings.

The proportion of diagnoses of bundle-branch block made at the bedside and substantiated by electrocardiograms is similar to that of the smaller series of 9 cases reported previously. (Table 2.)

TABLE 2.—FIFTY CASES OF BUNDLE-BRANCH BLOCK.

	No.	Per cent.
Diagnosed clinically	34	85
Not recognized clinically	4	10
Suspected: not definitely diagnosed	2	5
Number of diagnostic attempts	40*	100

Differential Diagnosis. Inasmuch as Hill was unable to find reduplication of the apex thrust by inspection and palpation and found reduplication of the first heart sound in only about one-fourth of his cases, it is natural that he was unwilling to make clinical diagnoses from insufficient data. Feebleness of the heart sounds or the presence of an apical systolic murmur were the commonest auscultatory signs in his series. It has likewise been our experience that faint, or indeed inaudible, sounds at the beginning of systole are frequently encountered and constitute a helpful diagnostic sign of blundle block. But this is one sign only and, as Hill points out, not characteristic of this condition alone. To establish a clinical diagnosis, the entire group of physical signs must be considered.

These signs are almost never encountered except in the presence of intraventricular block of some type, either complete bundle-branch block or a marked delay in intraventricular conduction. Certain cases of prolonged Q–R–S interval that do not show all the electrocardiographic features of bundle-branch block as defined by Carter[3] exhibit physical signs that are identical with those found in bundle-branch block. Presystolic gallop rhythm, for obvious reasons, may be mistaken for bundle block and *vice versa*.

Among 9 cases that exhibited a prolongation of the Q–R–S interval but lacked the complete electrocardiographic picture of bundle block, systolic reduplication at the apex was seen in 7 instances and felt in 5, while suggestive auscultatory evidences were distinguished in 6 instances. It is clear, therefore, that we cannot hope as yet to differentiate clinically between complete bundle-branch block and other forms of marked intraventricular delay. It is our impression, however, that the physical signs may be more marked and that they probably are more constant in cases of complete bundle

* Of the 10 remaining cases 6 were seen after the electrocardiogram was known, while in 4 other cases there was a difference of opinion as to the diagnosis. During the course of these diagnostic attempts the erroneous clinical diagnosis of bundle-branch block was made in 6 cases in which the electrocardiogram showed the condition not to exist.

block than in the other group. We have studied the physical signs systematically in 50 cases of complete bundle block but our series of other forms of prolonged intraventricular conduction is too small to be of real value.

Presystolic gallop rhythm is the condition most likely to simulate the clinical signs of intraventricular block. Four years ago, one of us (King) in an attempt to distinguish the two conditions, laid down the following hypothetical features thought to be characteristic of each: on inspection and palpation, *presystolic gallop* is indicated by an apparently presystolic, apical lift or shock preceding a ventricular impulse that is normally sustained; *intraventricular block* causes a split in the main ventricular lift. Thus, the adventitious impulse in presystolic gallop is comparatively slight and early, in intraventricular block it is late and follows the main systolic thrust. On auscultation, *presystolic gallop* causes a sound preceding a first sound that is usually vigorous or that is replaced by a vigorous murmur; in most cases of *intraventricular block*, the sounds begin with systole and consist of two faint sounds replacing the usual single first heart sound: either this is heard or the sounds are inaudible or are replaced by one or two murmurs. Applying these hypotheses to the diagnosis of 100 unknown cardiac cases (among which were 9 instances of bundle block and 12 of presystolic gallop) the one condition was mistaken for the other only once. Among 44 cases of bundle-branch block (Table 2) the incorrect diagnosis of presystolic gallop was made in 2 instances, and by one of two observers in 2 other cases. Among 14 cases of marked presystolic gallop, the correct clinical diagnosis was made in every instance.

Marked hypertension is considered to conduce to presystolic gallop rhythm. Certainly it is true that presystolic gallop rhythm, when present, is nearly always associated with marked hypertension and may disappear entirely during the moments of lowered tension that follow administration of drugs such as the nitrites and nitroglycerin. Definite apical reduplication in the presence of hypertension may indicate either presystolic gallop or intraventricular block. Reduplication in the presence of a normal tension would make us suspect the presence of intraventricular block. The diagnosis of block should not be withheld because of the presence of hypertension, however, provided typical signs be present. Thus, among the 50 cases of bundle-branch block reported in this series there was a systolic blood pressure of 150 mm. Hg. or above in 26 instances (52 per cent). Three of these 26 cases had complete *A–V* dissociation and idioventricular rhythm with the customary high systolic and low diastolic readings.

The blood-pressure readings of the 50 individuals in this series are tabulated above (Table 3). In practically every instance, a given figure represents the average of a large number of readings made while the patient was under observation.

TABLE 3.—BLOOD PRESSURE IN BUNDLE-BRANCH BLOCK.

Case No.		Blood pressure.	Case No.		Blood pressure.
1		250/150	22		155/85
2		240/80	23		150/80
3		225/100	24		150/60
4	First admission	220/110	25		150/45
	Second admission	210/128	26	In 1928	150/50
	Third admission	200/130		In 1929	150/40
5		190/110	27		146/90
6	First admission	190/100	28		145/104
	Second admission	100/60	29		140/81
7		190/110	30		135/85
8		190/100	31		105/75
9	First admission	190/70	32	In 1928	135/80
	Later	155/90		In 1929	130/90
10	First admission	185/100	33		130/98
	Levelled to	160/100	34		125/80
	Second admission	240/100	35		120/80
	Levelled to	160/100	36		120/80
	Third admission	180/110	37		120/90
	Fourth admission	170/100	38		120/70
11		180/140	39		118/75
	Later	160/130	40		116/95
12	First admission	180–220	41		116/95
		120	42	In 1928	115/70
				Second admission	120/75
	Second admission	117/98		Present admission	140/80
13		180/75	43		115/70
14		176/105	44		110/90
15		174/75	45		110/70
16		170/110	46		110/70
17		170/110	47		110/60
18		170/100	48		110/60
19		170/100	49		105/65
20		166/86	50		98/70
21		160/110			

Excluding the 3 instances in which there was also *A–V* dissociation with idioventricular rhythm, systolic pressures of 170 mm. Hg. or above occurred in 17 instances; and of 200 mm. Hg. or above in 5 instances. These figures which are somewhat lower than those recorded by Hill[7] and Herrick and Smith[6] may be accounted for by the averaging of a number of successive readings in this series. A number of cases which were followed over a period of several years showed gradually increasing pressure while in others there was a gradual lowering of the pressures usually associated with the development of myocardial failure.

In the group with presystolic gallop rhythm there was nearly always marked hypertension, readings of 200 systolic and 120 diastolic mm. Hg. and above being not uncommon.

In attempting to evaluate the significance of physical signs, more error has resulted up to the present time from leaning too far toward the diagnosis of presystolic gallop in hypertension than from mistaking presystolic gallop for bundle block. We feel that the two conditions are different both with regard to mechanism and clinical signs. This point will be discussed later.

In 3 cases with characteristic physical signs and electrocardiographic evidence of intraventricular block there was also complete auriculoventricular dissociation. These cases aided materially in the elucidation of the relation of such physical signs to events in the heart's cycle, inasmuch as the signs were found to be quite independent of auricular activity.

Case Reports. CASE 1.—(A. S. J. H. H. Disp. No. J-12153.) White, male, aged 60 years. There was no history of past infection. Symptoms consisted of dyspnea, orthopnea, edema and morning cough. Examination of the heart revealed marked visible and palpable reduplication of the apex thrust. During ventricular diastole there could be seen slight but definite rhythmic precordial waves due to the auricular contractions. (Demonstrated by Dr. L. V. Hamman.) The independent auricular waves were also visible in the jugular veins. The first heart sound was of fair quality, followed by a soft systolic murmur. The auricular contractions were audible. The radial pulse rate was 36 per minute; blood pressure, 220 systolic and 70 diastolic; rhythm of pulse regular. There was general arteriosclerosis. Teleoroentgenograms of the heart showed: M. R., 7 cm.; M. L., 10 cm.; T., 28. Wassermann reaction of the blood was negative. Clinical impression was: Bundle-branch block, complete auriculoventricular block, hypertension. Electrocardiogram showed: Complete *A–V* block. *Q–R–S* interval, 0.14 second. Right bundle-branch block. This was the first case of auriculoventricular block combined with bundle-branch block that came under our observation. It appears to be of special importance in showing that the signs of bundle-branch block are quite independent of auricular activity.

CASE 2.—(G. B. U. M. H.) A white male, aged 69 years, suffered from dyspnea, orthopnea and edema. There had been infection with syphilis 27 years previously. Examination of the heart showed a visible and palpable reduplication of the apex thrust. On auscultation a single first sound was distinguished, and this was followed after an appreciable interval by a systolic murmur. Pulse at the wrist was regular, 49 per minute. Teleoroentgenogram showed slight cardiac enlargement. Blood Wassermann reaction was positive; blood pressure, 174 systolic and 75 diastolic. There was evidence of arteriosclerosis and emphysema. Electrocardiogram showed complete auriculoventricular dissociation; *Q–R–S* interval, 0.11 second; all *R* waves notched; auricular rate, 88; ventricular rate, 49. *T* waves in opposite direction to the main ventricular deflection throughout. The *R* waves did not indicate predominance of either levogram or dextrogram. This patient was seen by one of us (J. T. K.) after the electrocardiogram was known, hence a purely clinical diagnosis could not be attempted. The case is of interest because it shows that the physical signs which we have found in bundle-branch block may occur in other types of intraventricular block, *i. e.*, in cases showing prolonged intraventricular conduction time without the electrocardiographic picture of typical bundle-branch block. The case also shows, as noted in Case 1, that the physical signs of intraventricular block are not related to auricular activity.

CASE 3.*—(G. B. J. H. H. No. 33820.) A male negro, aged 63 years, showed dyspnea, orthopnea and edema. He had pneumonia 29 years prior to admission and typhoid fever 21 years before. There was no other history of significant infection. Examination of the heart showed visible and palpable reduplication of the apex thrust, and definite reduplication

* This case is to be reported in full at a later date.

of the first heart sound, which was soft and faint. Auricular sounds were audible and auricular waves were seen over the precordium. Pulse was regular, rate 27 per minute. Blood pressure was 200 systolic and 80 diastolic; the blood Wassermann reaction was negative. Teleoroentgenogram showed: M. R., 5; M. L., 11.7 cm.; thorax diameter, 30 cm.; aorta dilated. There was generalized arteriosclerosis. Clinical impression before consulting electrocardiogram (D. McE.): Complete auriculoventricular block, bundle-branch block. Electrocardiogram showed complete auriculoventricular dissociation, predominant levogram, right bundle-branch block with Q–R–S interval, 0.14 second. At a later date there was a return to normal sinus rhythm with typical electrocardiographic evidence of right bundle-branch block. The clinical signs of bundle-branch block disappeared however. The reason for this is not apparent, but we observed this to occur in several cases that have been under observation for long periods of time. Hill[7] noted several similar instances in his series.

These 3 cases offer strong evidence that there is no necessary relationship between auricular contraction and the physical signs of intraventricular block. The second case suggests that such physical signs may be found in instances of prolonged intraventricular conduction time that do not show the complete electrocardiographic picture of bundle-branch block. A number of cases of this type have been met with.

In establishing the correctness of the clinical diagnosis in these cases, the electrocardiogram has been the final arbiter and, save for 5 instances referred to below, the criteria of Carter[3] have been strictly adhered to, viz.: (1) Prolongation of the intraventricular conduction time to 0.10 second or beyond; (2) slurring or splintering of the Q–R–S complexes;* (3) a predominant levogram or dextrogram; (4) T waves of opposite sign to the main ventricular deflection in Leads I and III.

The aforementioned 5 cases, included in the series of 50 cases, all of which were diagnosed clinically as bundle-branch block, exhibited electrocardiograms that were levograms and that satisfied all the above criteria save that slurring of the Q–R–S complexes was absent. The significance of such electrocardiograms is in debate at present. There would seem to be increasing evidence that curves of this type indicate block in the right bundle rather than simple left ventricular preponderance. Indeed, Luten and Grove[12] to whose paper the reader is referred for a discussion of the subject, consider that curves of this character, with Q–R–S of *normal* duration are indicative of impaired conduction in the right bundle. Without entering the polemic on the subject, we suggest that some value may reside in the clinical observation that, of 5 such cases, all exhibited the clinical signs of bundle-branch block.

* In view of the recent work of F. N. Wilson and his collaborators (P. S. Barker, A. G. Macleod and J. Alexander: Excitatory Process Observed in the Exposed Human Heart, Trans. Assn. Am. Phys., 1929, **44**, 125) it should be explained that the interpretation of electrocardiograms in this report has been made in conformity with the previous standard. For example, upright Q–R–S complex in Lead I and inversion of same in Lead III has been considered indicative of right-side block.

Of additional interest are 7 cases in which auricular fibrillation and intraventricular block were present coincidentally. It is reasonable to assume that auricular activity played no part in the production of the clinical signs of bundle-branch block in these cases. The correct diagnosis of bundle-branch block was made clinically in 5 of the 7 cases. On the other hand it is doubtful whether a typical presystolic gallop sound ever persists in cases of hypertension following the onset of auricular fibrillation.

In an effort to illustrate the reduplicated thrust in cases of bundle-branch block, attempts were made to obtain polygraphic tracings from the apex and from the carotid. It was hoped that in this manner it would be possible also to determine which ventricle was being activated first. After many trials, however, it was found that the apparatus failed to inscribe the mechanical events with sufficient rapidity. By fastening a light straw upon the chest over the region of the apex impulse, it was found that the phenomena occurring at the apex could be demonstrated easily in the movements of the straw. This has proved a valuable method of presenting the signs objectively before groups of students. It has been possible to record the double apical thrust graphically both by cinematograph and in apex cardiograms.

For the latter purpose, the patient was placed in the recumbent position between the galvanometer and the recording camera of a Hindle electrocardiograph, the chest was exposed and a light broom straw was fastened by adhesive tape or by plasticene to the chest wall in the region of the apex impulse. The straw intercepted the beam of light from the electrocardiograph and its shadow was recorded on the film beside that of the galvanometer string. Simultaneous mechanical and electrocardiographic records were therefore made upon the film with the benefit of the same time marker.

No accurate analysis can be made of the time relationship of the various mechanical events in the cardiac cycle as inscribed in such records. Even the cardiograms recorded optically with the more sensitive capsules of Frank have variable degrees of lag due to slow or inadequate transmission of the mechanical events in the heart to the tissues of the chest wall. For purposes of illustration, however, the apex cardiogram is of value and for this reason records were made on a number of normal individuals and on patients with bundle-branch block and with presystolic gallop rhythm. No difficulty was experienced in recording the phenomena when such were visible or palpable over the precordium.

Records from normal individuals were obtained with some difficulty owing to the indistinctness with which mechanical events in the heart are transmitted to the precordium. Such records showed monophasic and diphasic curves of low amplitude which commenced 0.05 to 0.15 second after the beginning of *R* and which were complete by 0.27 to 0.50 second after *R*. No bifid character was noted

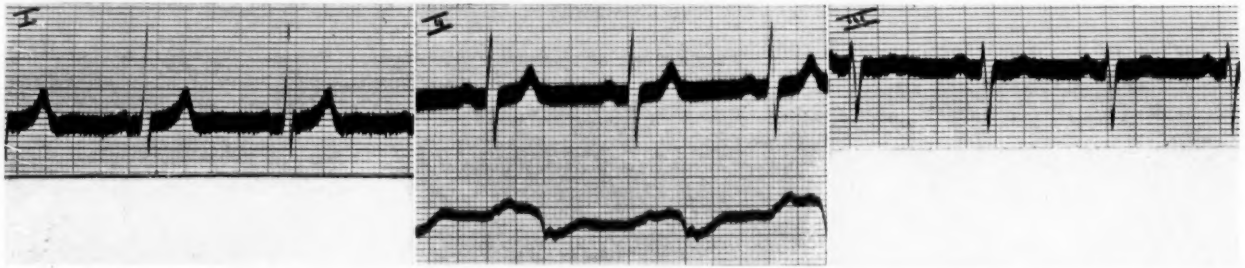

FIG. 1.—(8616.) Electrocardiogram and apex cardiogram (with Lead II) from control series. The subject was a male, aged 24 years, with rheumatic mitral stenosis and insufficiency and aortic insufficiency. No gallop rhythm. Electrocardiogram shows predominant levogram, *Q–R–S* 0.08 second. Apex cardiogram shows a normally sustained systolic plateau commencing 0.04 second after *R* and ending 0.42 second after *R*. The notch on descending limb was associated with a palpable diastolic shock apparently due to valve closure.

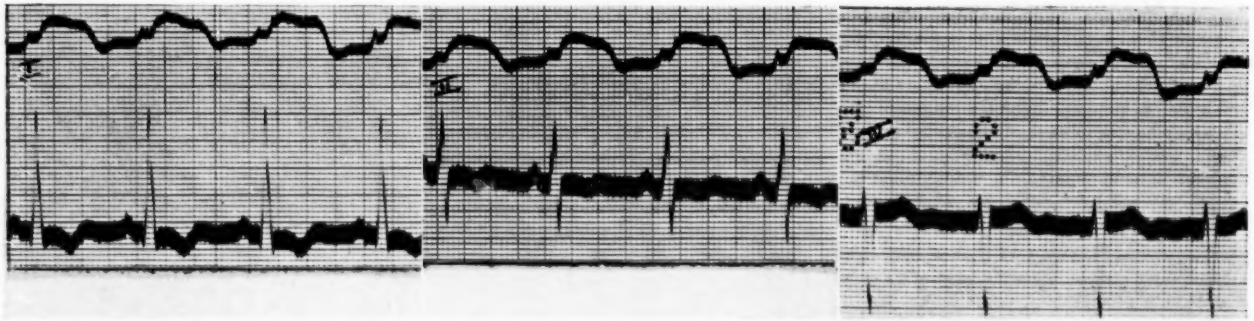

FIG. 2.—(8779.) Electrocardiogram and apex cardiogram from a patient with presystolic gallop rhythm. Blood pressure, 240 systolic and 140 diastolic. Electrocardiogram shows predominant levogram. *Q–R–S*, 0.1 second; *T*, I inverted; *T*, III upright. Cardiogram shows a series of high and long positive hummocks. On the upstroke of each there is a short positive deflection. This commences 0.02 to 0.03 second before *R* and is complete at 0.02 second after *R*. The further abrupt rise of the hummock commences 0.08 second after *R*. The hummock ends 0.52 to 0.56 second after *R*.

FIG. 3.—(8943.) Electrocardiogram and apex cardiogram from patient with presystolic gallop. Blood pressure, 186 systolic and 160 diastolic. Electrocardiogram shows *Q–R–S*, 0.08 second. Slight slurring of *Q–R–S* in all leads. *T*, I upright; *T*, II and III biphasic. Apex cardiogram shows series of long negative waves preceded by a sharp negative deflection which commences 0.07 second before *R* and is complete by 0.03 second after *R*. The systolic plateau then commences and persists until 0.52 second after *R*.

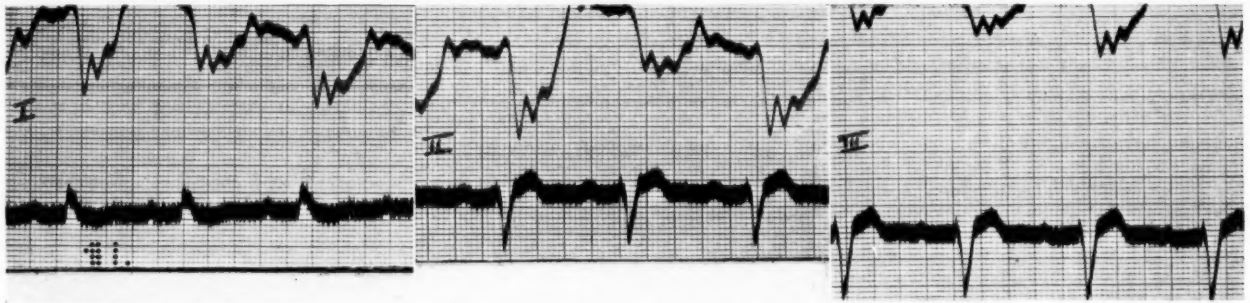

FIG. 4.—(6295.) Electrocardiogram and apex cardiogram from patient with right bundle-branch block. *Q–R–S*, 0.13 to 0.14 second. Cardiogram shows reduplication of the large negative systolic wave.

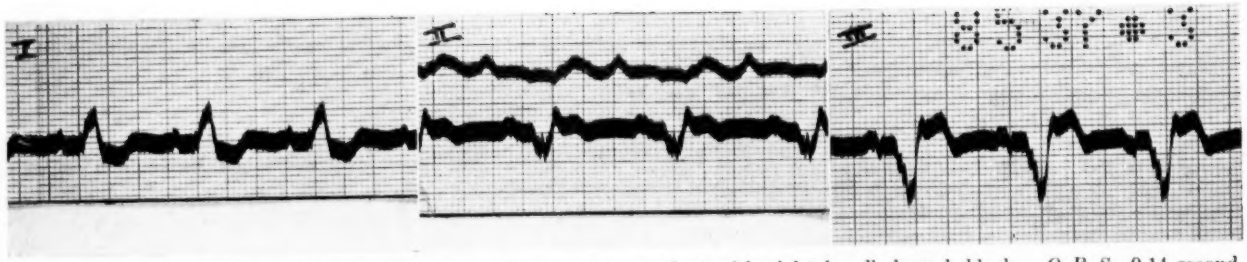

FIG. 5.—(8537.) Electrocardiogram and apex cardiogram from patient with right bundle-branch block. *Q–R–S*, 0.14 second. Cardiogram shows series of long positive waves of bifid character. First component commences 0.1 second after *R* and lasts until 0.45 second after *R* when the second component commences and lasts until 0.65 second after *R*.

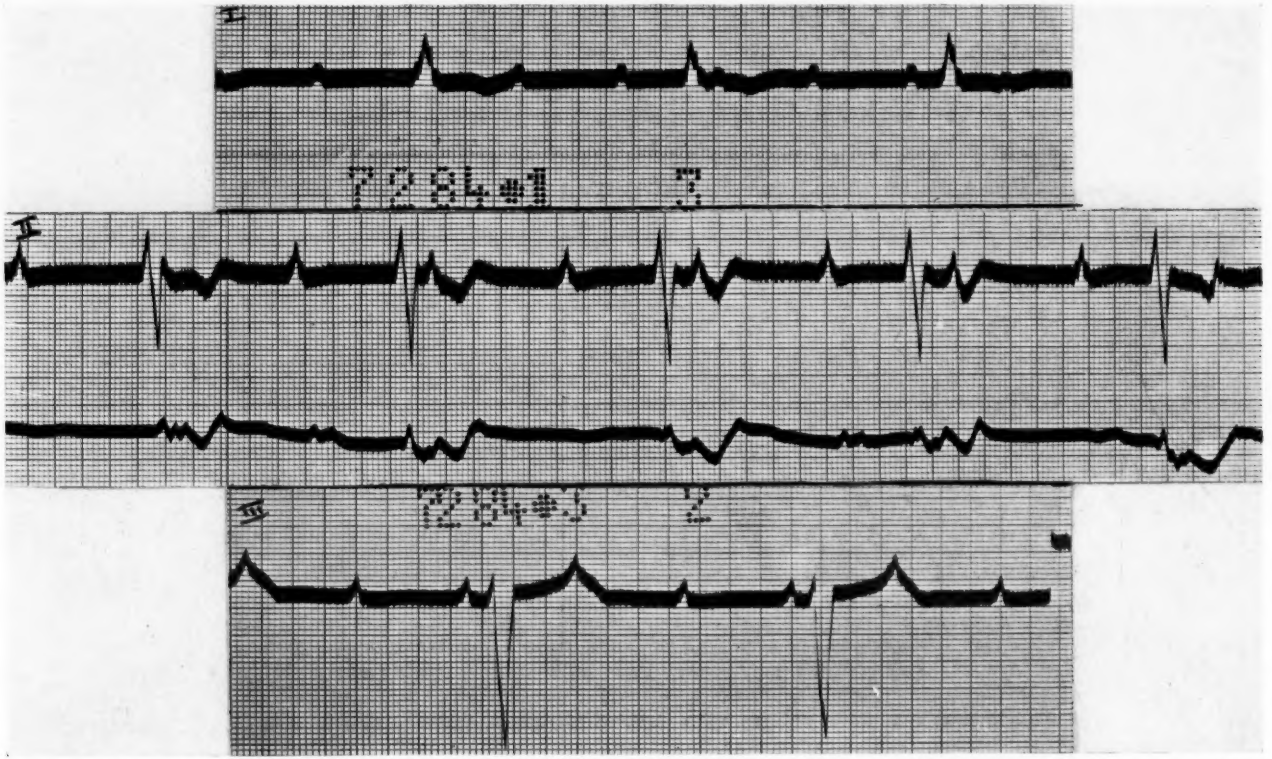

FIG. 6.—(7284.) Electrocardiogram and apex cardiogram of patient (Case 2) with right bundle-branch block and complete auriculoventricular dissociation. *Q–R–S*, 0.15 second. Auricular rate, 86. Ventricular rate, 29. Cardiogram shows a series of bifid, negative deflections associated with ventricular activity and commencing 0.06 second after *R*, the second component of each wave commences 0.26 second after *R* and is complete 0.6 second after *R*. Auricular waves can be seen. The fourth and fifth ventricular complexes (Lead II) of the cardiogram are entirely dissociated from auricular activity.

in the sustained apical wave during ventricular systole in any instance (see Fig. 1).

Presystolic Gallop. In this series of patients with presystolic gallop, the presystolic deflection of the straw could not be demonstrated in every instance. It was shown to be present, however, in those cases in which gallop was visible or palpable on the chest wall. No reduplication of the systolic thrust was noted in any instance. When seen, the presystolic deflection appeared 0.02 to 0.06 second before *R* and was complete by 0.02 second before *R* to 0.04 second after *R*. These deflections were similar to those visible and palpable upon the chest wall and, whatever their cause, occurred prior to the electrical evidence of systole. Figs. 2 and 3 are characteristic examples of these curves.

Bundle-branch Block. So far as we are aware, no attempt has been made to demonstrate the double apex thrust in bundle-branch block by means of apex cardiograms in a series of cases. The cardiograms of the individual cases reported by Kauf[8] and by Eppinger and Stoerk[5] show, however, bifid systolic waves. In the present series, apex cardiograms, in every instance save one, showed a double reflection which occurred during systole and which was indicative of the reduplicated systolic thrust visible to the naked eye during systole. The first component of this double systolic deflection commenced 0.06 to 0.10 second after *R* and lasted until 0.17 to 0.45 second after *R*, when the second component of the systolic deflection commenced and lasted until 0.44 to 0.62 second after *R*.

Typical curves are seen in Figs. 4 and 5. Of particular interest is the record Fig. 6 obtained from Case 1 (reported above) in which there was complete *A–V* dissociation and right bundle-branch block. In this case it was possible to demonstrate in the apex cardiograms not only the double systolic deflection associated with ventricular systole, but also the individual auricular beats which were transmitted to the apex as small rhythmic waves. The latter bore no constant relation to the ventricular deflections. It is not possible, therefore, to consider that contraction of the auricles is in any way responsible for the bifid character of the apical wave during ventricular systole.

Lewis[11] has recorded reduplication of the first sound in 4 cases of intraventricular block and has discussed its time in the heart's cycle. The beginning of the extra component was presystolic in each instance. What the relation of this sound reduplication to the waves on the precordium may be remains to be determined. One is tempted to attribute the waves noted in the present report to a theoretical asynchronism of the ventricles resulting from delay of the impulse to one ventricle. We have no proof of this, however, and we prefer simply to conclude that the signs we have discussed may occur independent of auricular systole and that they are due to some peculiarity of ventricular activity in the presence of intraventricular block.

It has been pointed out above that no attempt has been made to analyze accurately the relationship of these phenomena nor to ascribe their production to any definite mechanism. The records do, however, show that no reduplication can be demonstrated in normal individuals, that visible presystolic gallops occur in presystole and that the divided apex thrust visible in a large percentage of cases of bundle-branch block is associated with systole. Such phenomena can be recognized by the naked eye but are here illustrated in graphic form.

Cinematographic Demonstration. An attempt was first made to record the visible double cardiac impulse of patients with intraventricular block by means of motion pictures of the precordial area. This was found to be impracticable, as the reduplication could not be seen in the picture even in cases in which it was readily made out by direct inspection of the precordium. A method was, therefore, used which consisted in placing a straw over the precordium as previously described, casting a beam of light upon it and recording the shadow of the moving straw as it fell upon the eye of the cinematographic camera. The film shows the movement of the straw as it is deflected by each cardiac impulse.

As controls, 6 normal medical students were selected. In some, the movement of the straw was slight, in others, of fair amplitude.

Five cases of bundle-branch block were then studied by this method. The first case was that of the patient recorded above as Case 1, in which complete auriculoventricular block coexisted with bundle-branch block. The movement due to ventricular contraction is distinctly reduplicated, between the ventricular contractions may be seen slight but definite movements of the straw that are doubtless associated with auricular contraction. In the other cases, simple bundle-branch block was present and in each case the motion of the straw as shown by the film is reduplicated and may be distinguished readily by the naked eye. These patients were not selected but were studied because they happened to be available at the time the film was made. It seems significant that the double movement may be made out in each of these unselected cases: however, there are probably obese individuals who might prove unsatisfactory for this method of demonstration.

Summary. An analysis of 50 consecutive cases of bundle-branch block showed the following physical signs: visible reduplication of the apex thrust in 42 (84 per cent), palpable reduplication in 40 (80 per cent); the first heart sound was split into two elements in 28 (56 per cent), there were two separate systolic murmurs in 6 (12 per cent) and a single first sound with a separate murmur in 8 (16 per cent).

On the basis of these signs a correct diagnosis was made prior to knowledge of the electrocardiogram in 34 of 40 attempts (85 per cent); the presence of bundle-branch block was suspected in 2 (5 per cent) but was not definitely diagnosed; the diagnosis was not

made in 4 (10 per cent). There was a difference of opinion in 4 other cases. In the remaining 6 cases, the presence of bundle-branch block was recognized only by electrocardiogram.

In 3 patients showing complete auriculoventricular block as well as intraventricular block, the diagnosis of both conditions was made in 2 cases from clinical signs and the signs were equally clear in the third case; signs of bundle block were found and this condition recognized clinically in 5 of 7 patients showing both fibrillation and bundle block. The latter two groups of cases show that the auricles are not concerned with the physical signs of bundle block.

Presystolic gallop bears a superficial resemblance to the signs of bundle block: however, clinical evidence and apex cardiograms show the two conditions to be different; presystolic gallop being truly presystolic, the signs of bundle block being limited to systole and causing a division of the apex systolic plateau. Normal controls failed to show systolic reduplication.

A cinematographic film of the movement of a straw attached to the cardiac apex showed a double systolic thrust in each of 5 consecutive cases of bundle-branch block.

Conclusions. 1. Intraventricular block may be recognized in a majority of cases from physical signs.

2. The most constant signs consist of visible and palpable reduplication of the apex thrust.

3. The reduplication is within systole. The auricles play no part in the production of the physical signs.

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AN UNUSUAL ATROPIN EFFECT ON VENTRICULAR TACHYCARDIA.

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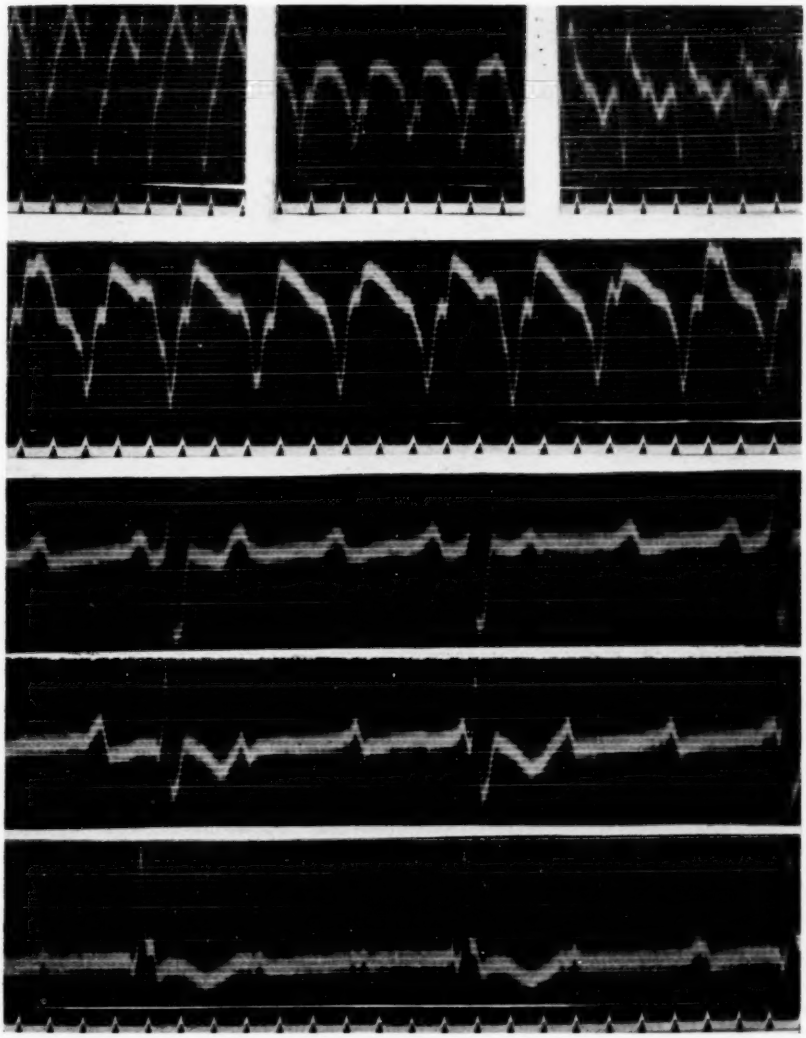
It is generally accepted that certain disturbances in the auricles of the heart, such as auricular fibrillation and auricular flutter, are due to a circus movement.[3] The most important factor in maintaining this circus seems to be the length of the refractory period of heart muscle. Influences that shorten the refractory period serve to perpetuate the circus and contrariwise, those that lengthen the refractory period tend to abolish the circus. There is a growing impression that tachycardia, ventricular in origin, is due to a similar circus movement in the ventricles. Much has been written concerning both experimental and clinical effects of quinidin on disturbances of this nature. Although quinidin has a double and conflicting action it often abolishes these movements. One effect of quinidin is to lengthen the refractory period which would tend to abolish it, while the other is to slow the speed of the impulse which would tend to maintain the circus. When the former predominates normal rhythm is established. Quinidin has been found to be frequently effective in restoring the normal mechanism in cases of ventricular tachycardia which, as has been stated above, is quite likely due to a circus movement in the ventricles.[2] It has been found also that atropin, mainly through its paralyzing effect on the vagus, lengthens the refractory period of the auricle and thereby tends to abolish the circus motion.[4] The case reported below illustrates first, a partial effect of quinidin and second, a most striking and unique result of atropin on ventricular tachycardia.

Case Report.—A man, aged 56 years, entered the Hospital on May 12, 1928, in a typical attack of coronary thrombosis. An electrocardiogram taken on admission showed a ventricular tachycardia with a rate of 168. Quinidin sulphate was given in large doses and the tachycardia was slowed repeatedly but never below 108, as shown by repeated electrocardiograms. Following these temporary reductions in rate, it invariably rose again to 160 or 170. After 11 days of this sort of medication it was decided to try atropin, at a time when the ventricular rate was slowed to about 115 by quinidin, on the theory that by removing vagal effect the resulting increase auricular rate would enable the auricle to resume its control as the pacemaker. It was thought that if the auricular rate could be increased to a level greater than the ventricular a normal sequential rhythm might be restored. Accordingly, 0.002 gm. of atropin sulphate was given subcutaneously. The result was surprising. Within 7 minutes after the injection the pulse fell from a rate of 115 to 30 beats per minute. An electrocardiogram at this time uncovered a complete heart block with a ventricular rate of 30 and an auricular rate of 98. The heart sounds were distant and



Upper three tracings are Leads I, II, III, taken May 20, 1928, and show ventricular tachycardia with a rate of 180. The strip below this is Lead II taken May 22, 1928. The ventricular rate has been slowed to 115 by quinidin although tachycardia perists. Lower curves are Leads I, II, III, taken 7 minutes after 0.002 gm. of atropin had been injected and 30 minutes after previous tracing. They show complete heart block with an auricular rate of 98 and a ventricular rate of 30.

the patient was cyanotic and *in extremis* to such a degree that repeated doses of caffein sodiobenzoate were given. The ventricular rate remained between 30 and 35 for 27 hours and was then suddenly found to be 160 again. Following this the ventricular rate fluctuated between 25 and 190, despite two more trials of atropin and interrupted doses of quinidin, until the 16th day after admission. From this time on the rate did not fall below 130. The patient finally developed a bronchopneumonia and died 34 days after the onset of his attack.

This unusual atropin effect was entirely unexpected. When it was found that the patient had complete heart block it became clear that a normal sequential beat from auricle to ventricle was impossible. This result from atropin therefore must have been due to its action on the ventricle either through a direct effect on the muscle or indirectly through the vagus. There is experimental evidence to show that atropin through its paralyzing effect on the vagus increases the refractory period of auricular muscle[4] and thereby might break up a circus rhythm. It is felt that this may well have been the mechanism involved in this case, although Drury[1] found that vagal stimulation did not shorten the refractory period of the dog's ventricle. If this is not the explanation of the atropin effect in the above case, it brings up for consideration the possibility of a direct action of atropin on ventricular musculature. It is also inferred that if the conduction apparatus had not been involved in the coronary attack, the ventricular tachycardia might likewise have disappeared under atropin with a restoration of normal rhythm. The unusual effect obtained from atropin in this case suggests that it might serve as an additional aid in restoring normal rhythm where a circus movement fails to respond to quinidin alone.

Summary. A case of coronary thrombosis was observed showing ventricular tachycardia with a rapid ventricular rate. The ventricular rate was frequently slowed by increasing doses of quinidin to 110 or 115, but the tachycardia could not be abolished. Immediately following 1 dose of 0.002 gm. of atropin sulphate this abnormal mechanism disappeared, uncovering complete heart block with a slow idioventricular rhythm. It is believed that the circus movement was broken up by atropin through its paralyzing effect on the vagus.

NOTE.—I wish to express my indebtedness to Dr. S. A. Levine for his aid in the preparation of this paper.

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CONGENITAL HEART DISEASE WITH MULTIPLE CARDIAC ANOMALIES.

Report of a Case Showing Aortic Atresia, Fibrous Scar in Myocardium and Embryonal Sinusoidal Remains.

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We are reporting this single case of congenital heart disease because of the unusual number of congenital anomalies that it presented. The defects seen are not only numerous but some of them are distinctly rare.

Case Report. We know practically nothing concerning the history of the child or its parents. The child lived only 12 hours and necropsy examination was limited to the heart which was obtained by us with all the vessels cut quite close to the cardiac chambers.

Pathologic Examination. Except for a slight enlargement in the transverse diameter the heart is about normal in size. The longitudinal diameter measures 3.6 cm., the transverse 2.9 cm. The heart is divided by the interventricular groove into a large right, and a small left portion. The right ventricular chamber is considerably dilated; its wall measures 2.5 to 3 mm. in thickness in its lateral and apical portions; toward the base it becomes thicker, measuring 6 mm. The tricuspid valve is normal. The right auricle is also dilated but otherwise normal. The foramen ovale is completely closed. The fossa ovalis is very small and its markings almost completely obliterated. The type of closure with fibrous puckering would indicate that the closure had taken place early in fetal life. The pulmonary artery, which is enlarged for an infant of this size, issues from the right ventricle in its normal position. It measures 1.7 cm. in circumference and contains 3 normal cusps.

The left ventricle consists of a small chamber, closed on all sides except for its communication with the left auricle by an extremely narrow isthmus measuring 1 to 2 mm. in diameter. The boundaries of this chamber can be definitely outlined on the epicardial surface by the anterior and posterior interventricular grooves. The left ventricular muscle is about twice as thick as the right, measuring 7 mm. over its entirety. The width of the left ventricular wall diminishes the lumen of this small chamber to the size of a cherry stone so that its total contents could not exceed ½ cc. On the cut surface of the left ventricular wall, varying in width from a fraction of a millimeter to half the thickness of the myocardium is a grayish-white area which is clearly demarcated from the normal muscle. It apparently consists of fibrous tissue which extends into the myocardium. Sections taken from histologic examination, will be described later.

The aorta is completely atresic. The ascending arch measures 2 to 3 mm. in circumference. The orifices of the coronary arteries open from its lower portion. At this level the lumen of the aorta tapers down rather suddenly

and immediately below this point it closes so that there is absolutely no communication with the left ventricle. The distal end of the aorta, although narrow, remains patulous. Its connections were unfortunately lost in the removal of the specimen. The ductus arteriosus could therefore not be examined. Two tiny budlike processes observed in the lower portion of the aorta near the point of origin of the coronary arteries are apparently the remains of the aortic valves.

The left auricle, like the left ventricle, is also small. It is about one-fifth the size of the right auricle. Attached to the left auricle by an isthmus is a very large left auricle appendage, the lumen of which, however, is rendered quite small by reason of a marked thickness of its wall. Entering the auricle are 4 pulmonary veins posteriorly and 1 vessel anteriorly, the connections of which cannot be definitely determined.*

The mitral valve is small, hypoplastic, and of entirely different appearance from that seen in the normal heart. It forms a diaphragm separating the diminutive auricle from the ventricle and the only communication between these two chambers is in the extreme anterior portion where the valve is deficient over a passage 1 to 2 mm. wide. There is no differentiation into anterior and posterior leaflets and no papillary muscles are observed. Two sets of what are apparently remains of chordæ tendineæ are, however, present.

Histologic Examination.—Left Ventricular Wall. Several specimens were taken from the left ventricular muscle in the region of the fibrous scar. The epicardium is moderately congested. The myocardium is of the infantile type but otherwise shows nothing unusual. The interesting feature was the presence of a zone of fibrous tissue extending from the endocardium into the muscle and varying in depth from about 0.5 mm. to ½ the entire thickness of the wall. It seems to have a folding tendency, invaginating by many finger-like processes into the heart muscle. There is nothing unusual about this type of fibrous tissue. It is rather loose, and contains stellate and oval-shaped nuclei. A myxomatous structure is occasionally seen while in other fields a hyalinized sclerosis is present. The demarcation between the fibrous tissue and the heart muscle is not clear cut due to the extension of small threadlike processes into the myocardium for some distance.†

Another remarkable feature of this case is the presence of numerous circular and oval-shaped channels in the left auricular appendage and left ventricle, which at first we interpreted to be branches of the coronary artery. In some, the walls are thickened without great reduction in the size of the lumen; in others the lumen is reduced to a mere slit. Most of them contain erythrocytes and all are lined by a thin layer of endothelium. On closer examination and further study by serial section we decided that they were the remains of the sinusoids of the embryonic heart. Many can be traced to an endocardial origin, some apparently developing as infoldings or invaginations of the endocardium. The possibility of their being arteries was ruled out by their rather large numbers, large size, wall structure unlike arteries, and their presence chiefly in the inner half of the myocardium (a location where one would expect few coronary vessels). Moreover, section of the main coronary vessels and their branches show normal arterial structure. The thick walls which surround some of these spaces resemble very closely the thick, fibrous wall of the endocardium; the fibrous tissue

* It has been suggested that this vessel possibly communicated with the superior vena cava, as in the case of McIntosh.[17]

† Syphilis was considered as a possibility in the causation of the pathology noted. However, no evidence of syphilis could be observed in the sections, a diagnosis that was confirmed by the late Dr. Warthin, Professor of Pathology, University of Michigan, who kindly examined these sections for us.

is of a uniform character and there is no differentiation into intima, media, and adventitia. The fibrous tissue surrounding the walls of these spaces merges imperceptibly with the interstitial fibrous tissue of the myocardium. These channels which are the remains of a sinusoidal circulation, normally found between the muscle columns during an early stage of development of the heart, resemble to a great degree the findings observed in a heart described by Grant.[7] Two small branches of the coronary arteries were traced by serial section to their union with a definite sinusoid (Figs. 6 A to E). The adventitia and media gradually blended with undifferentiated fibrous tissue, so that at the union of the sinusoid the original arteriole structure had largely disappeared. The intima and a few smooth muscle fibers are however preserved until the union with the sinusoid. Thus it appeared that blood passed through them from the coronary arterioles to be delivered to the cavity of the left auricle and ventricle (modified Thebesian system).

Left Auricular Appendage. The wall is unusually thick, and is composed of numerous interlacing muscular bundles widely infiltrated by fibrous tissue. Most of the latter can be traced as extensions from the thick fibrous wall of large blood spaces that appear to be anomolous vessels, but which are really infoldings of the thickened fibrous endocardium of the appendage. The blood spaces are apparently of the same type as those seen in the left ventricle.

Section of the coronary arteries reveals them to be normal. The right ventricular wall and right auricle present no abnormalities.

Summarizing, this specimen shows the following anomalies: Atresia of the Aorta, Hypoplasia of the Left Ventricle with marked Thickening and Localized Fibrosis of its Wall, Premature Closure of Foramen Ovale, Dilatation of Right Auricle and Vertricle, Diminutive Left Auricle, and Remains of the Sinusoids of the Embryonic Heart.

Course of Fetal Circulation in Aortic Obstruction. During fetal life the circulation is but little impaired by aortic stenosis. With stenosis of the aorta a smaller and smaller amount of blood will flow into the left atrium and to an increasing degree through the right ventricle. Therefore, the right ventricle, by reason of its increased work, will develop more quickly than the left ventricle which lags behind. With complete atresia of the aorta, the ascending aorta functions only as a coronary vessel from the aortic arch, and the blood can reach the aorta only through the pulmonary artery by the ductus arteriosus. There then exists in the words of Rauchfuss,[20] "one main chamber, the right ventricle, and one main arterial stream, the pulmonary artery." During these conditions, there is no noteworthy disturbance of the fetal circulation.

The disturbances in circulation begin with the taking of the first breath. With the inflation of the lungs a considerable amount of blood is directed toward the left ventricle. Since it is unable to go either through the aorta or through a patent ventricular septum, and since the foramen ovale is also closed, the blood remains stagnant in the left heart. This results in pulmonary congestion, pulmonary edema, and death.

Circulation in Aortic Obstruction After Birth. While unfortunately some of the vascular connections were lost in the removal of our specimen, it is possible in the light of what is known of similar cases

FIG. 1.—Anterior surface of the heart (actual size). The line in black represents the interventricular septum. *R. A.*, right auricle; *R. V.*, right ventricle; *L. A. P.*, left auricular appendage; *P. A.*, pulmonary artery (opened.)

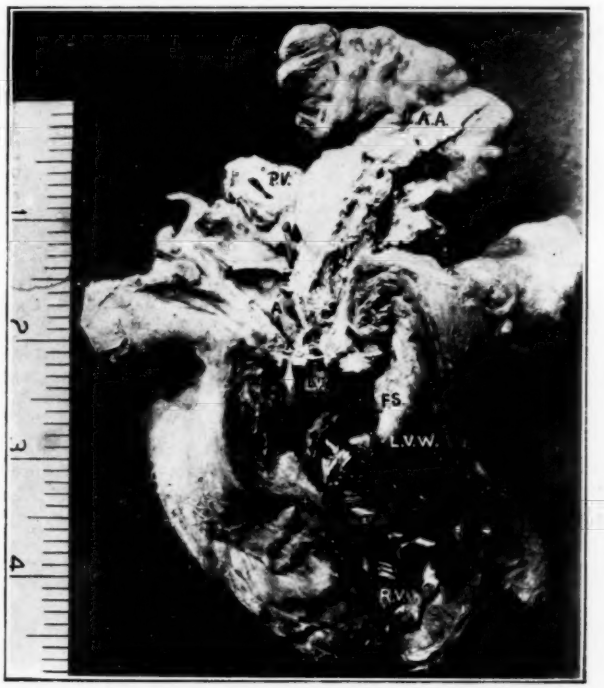

FIG. 2.—The heart cut open from the left margin. The section opens not only the left ventricle but also the right ventricle in its lower half. The diminutive aorta has been slit open. *L. A. A.*, left auricular appendage; *P. V.*, pulmonary vein; *A.*, aorta; *X.*, lower end of aorta closed, does not communicate with ventricle; *L. V. W.*, left ventricular wall; *L. V.*, left ventricle; *F. S.*, fibrous scar in wall of left ventricle; *R. V.*, right ventricle forming apex and lower half of left margin of heart.

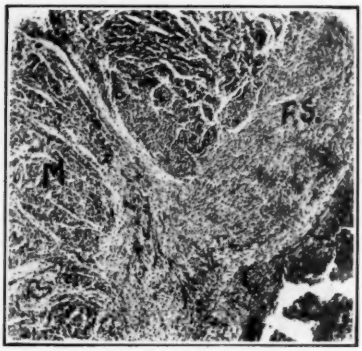

FIG. 3.—A section of the subendocardial scar in the left ventricle. Note the fibrous infiltration of the myocardium (×69). Many such extensions were noted. M., myocardium; *F. S.*, fibrous scar.

FIG. 4.—The inner half of the myocardium, showing numerous sinusoids (*S*). (×69).

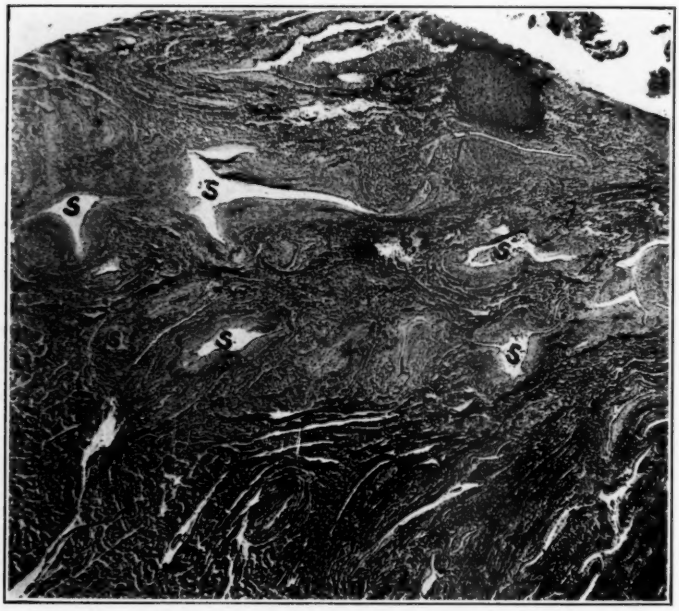

FIG. 5.—Several sinusoids with thick fibrous wall surrounding them (×30).

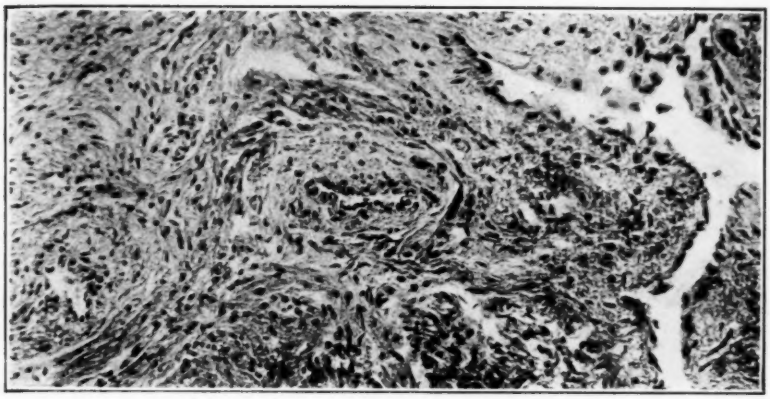

FIG. 6*A*

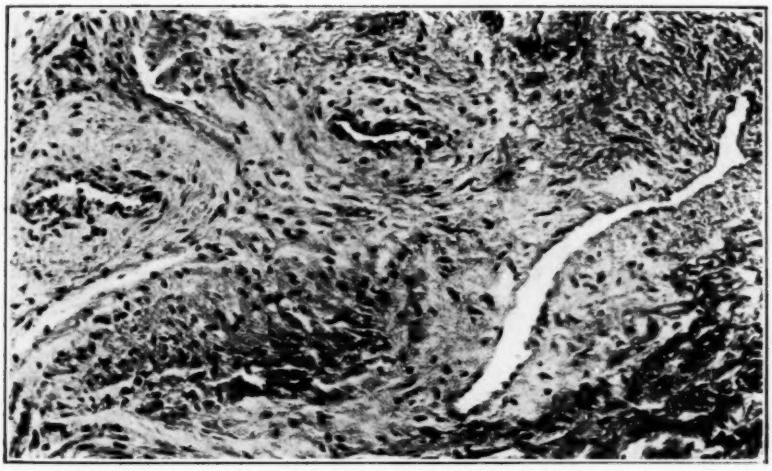

FIG. 6*B*

FIG. 6.—This figure is composed of five representative selections from serial sections showing the union of an artery with a sinusoid; *A*, shows the sinusoid (*s*) and two branches of the coronary artery (*A*). The arteries have a well-defined intima and media. The adventitia is not clearly defined in this picture (×177); *B*, the media of the arteries is beginning to lose its characteristics and tends to blend into the surrounding tissue (×177); *C*, in this figure only the intima is clearly defined. The media and adventitia are indistinguishable from the surrounding tissue. One artery is approaching the sinusoid (×177); *D*, this artery is now separated from the sinusoid only by a thin wall of tissue (×177); *E*, union has occurred between the artery and the sinusoid. Note that the part that represents the artery is still lined with intima (×177).

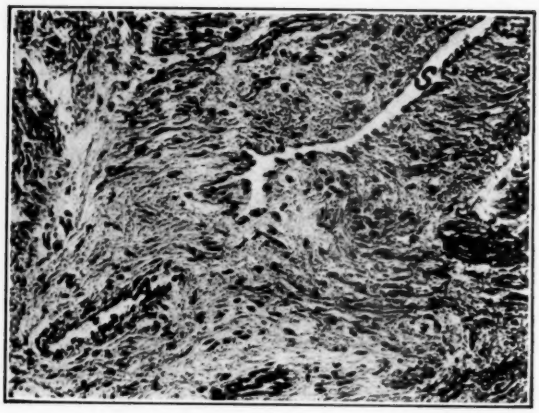

FIG. 6*C*

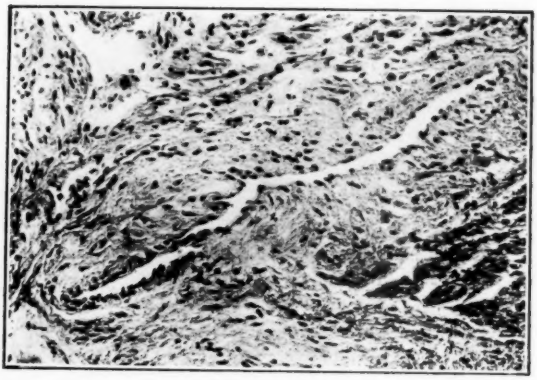

FIG. 6*D*

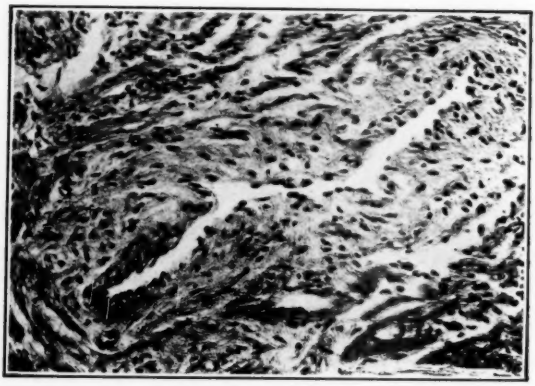

FIG. 6*E*

to reconstruct the probable course of the circulation. Venous blood entering the right auricle could not mix with that of the left auricle since the foramen ovale was closed. It therefore all proceeded into the right ventricle. From here the blood passed into the pulmonary artery, one branch of which went to the lungs, the other with the patent ductus, became the descending aorta. The body was, therefore, nourished practically entirely by venous blood. From the lungs blood reached the left auricle through the pulmonary veins. The fifth vessel of the left auricle may have communicated with the right heart in some manner, *e.g.*, with the superior vena cava as in the case of McIntosh,[17] thus permitting the blood to leave the left auricle. A small amount of blood passed into the left ventricle from the left atrium but could not leave the former chamber through its normal openings. The only possibility of egress was back into the left atrium through the incompetent mitral valve. The complete closure of the ventricular and auricular septum prevented the admixture of arterial and venous blood. In our case the only possibility for this to occur was the communication of the fifth vessel in the left atrium with the right heart. However, this amount of blood would have been quite small. The multiple anomalies presented by this case were of such a nature as to be practically incompatible with life.

The duration of life in all cases of this type has been very short. Most live but a few hours or days after birth. Occasional cases have been reported which have lived several weeks.

This case can be discussed from three chief viewpoints: (*a*) Aortic Atresia; (*b*) Fibrosis of Myocardium; (*c*) Remains of the Sinusoids of the Embryonic Heart.

Aortic Atresia. We will discuss first the aortic atresia, since upon it is dependent the small left ventricle and with it is often associated fibrosis of the myocardium. Rauchfuss[20] (1878) collected 18 cases of aortic atresia with closed ventricular septum: 3 of his own and 15 of others. In all of his cases the foramen ovale was patent. Other cases have been reported by Ruge[21] (2 cases), Shattock,[22] Meyer,[18] Haranger,[9] Eppinger,[3] Klepstein,[13] Jurgen,[11] Theremin,[25] (15 cases) Kaiser,[12] von Zalka,[26] Ganeff,[5] Bergman[2] and Hastings.[10] Abbott[1] in her text in Osler's Medicine (1927) encountered aortic atresia 7 times in 850 cases of congenital heart disease, an incidence of (0.8 per cent). Of the total number of 50 cases of aortic stenosis and atresia collected by Ruge[21] up to 1905, in only 5 cases was the foramen ovale completely closed as in our specimen.

Theories of Origin. Most writers, who have had similar cases, are of the belief that the origin of aortic atresia rests upon an infectious basis resulting in inflammation of the endocardium and the aortic valves, early in fetal life. This belief is based upon (*a*) the appearance of the aortic leaflets and the endocardium which resemble inflammatory processes observed in postnatal life; (*b*) the occa-

sional finding, as in the case of Klepstein,[13] of fresh vegetation on the aortic leaflets; (*e*) the occasional observation of lymphocytic infiltration of the myocardium in instances of aortic and pulmonary atresia (cases of B. Fischer[4] and von Zalka[26] (2 cases) and (*d*) the frequent presence of fibrosis of the myocardium (cases of Stiassny,[23] Mönckeberg,[19] Fischer,[4] Kochel,[14] Ganeff,[5] Ruge,[21] von Zalka.[26]) In only 3 of the 50 cases of aortic stenosis and aortic atresia gathered by Ruge[21] in 1905, were all indications of fetal endocarditis absent. Rokitansky (quoted by Ruge[21]) was of the opinion that aortic atresia may also arise by unequal division of the truncus arteriosus through anomalous position of the aortic septum. This would result in a small portion being reserved for the aorta with the production of stenosis or even atresia of its lumen.

In our case, the presence of considerable localized areas of subendocardial fibrosis in the left ventricle and left auricular appendage, is suggestive of inflammation. We do not believe, however, that this finding alone is necessarily indicative of a previous inflammatory process; it might conceivably result from such a process as interference with blood supply, a condition which was certainly present in our case. The type and extent of the fibrosis in this case can be said to have been modified by a collateral circulation through the sinusoidal system.

Abbott[1] in 1 case observed calcification with cellular infiltration and a diffuse fibrosis which was often "myxomatous in character recalling Warthin's description of focal fatty degeneration associated with localized colonies of spirocheta pallida." She believes that syphilis plays a great rôle in the production of these changes. Gräfenberg[8] has investigated numerous anomalies with reference to the presence of spirochetes. Although he found spirochetes in the viscera of 2 infants born with anomalies, in 22 other well-investigated cases no spirochetes were found. He concluded that syphilis plays a minor rôle in the causation of congenital anomalies.

The presence of myocardial changes with the formation of fibrosis in connection with aortic stenosis and atresia and pulmonary atresia is noted in the articles of Stiassny,[23] Mönckeberg,[19] Fischer,[4] Kochel,[14] Ganeff,[5] Ruge,[21] and von Zalka.[26] Von Zalka studied the myocardium in 14 cardiac anomalies, 8 of which were due to arrest of development and 6 were due to stenosis or atresia of the pulmonary or aortic orifices. In every one of the latter he found the myocardial changes above described.

According to Rauchfuss,[20] the beginning of the disease during fetal life may be approximately determined by the size of the left ventricle. The smaller and more rudimentary the left ventricle the earlier is the narrowing of the aortic ostium produced. With narrowing and closure of the aorta in midfetal life we find a supplementary recess or space of the right ventricle which is due to its enlargement about and beneath the diminutive left ventricle, the

right chamber thus forming the apex of the heart. In atresia occurring in early periods of fetal life the right ventricle appears to be more generally enlarged and the left ventricle is smaller. Based on the description of this author, the atresia in our case probably occurred in the fifth month of fetal life.

Premature Closure of the Foramen Ovale. In our case the foramen ovale was early closed. (See reasons given above.) The premature closure of the foramen ovale is explained by Rauchfuss[20] as follows: In the course of the circulation of the fetus, the blood from the inferior vena cava goes through the patent foramen ovale to the left atrium and then to the left ventricle and finally to the aorta to nourish the head. With progressive stenosis of the aorta during fetal life, a stage is reached when the pressure relationships are about equal in both auricles, because of stasis of the blood in the ventricle with insufficiency of the mitral valve. When this moment is reached the foramen ovale will close in the fetus since the condition for its remaining patent, namely, the flowing of blood from the right into the left auricle, has ceased to exist. Rauchfuss[20] however, states that with atresia of the aorta the pressure on the foramen ovale from the left atrium is sufficient to reopen it if it has not completely closed, and distend its wall to the right. However, in the total of 50 cases of aortic stenosis and atresia collected by Ruge[21] the foramen ovale was closed in only 5 cases. Why the foramen ovale closes in some and not in others is not definitely known. However, it is probable that if the pressure relationships are such as to permit closure to be maintained for some time fibrosis of such degree will occur that it cannot be later reopened.

Remains of Sinusoids or Intratrabecular Spaces of Embryonic Heart. The persistence of the intertrabecular spaces after birth is an extremely rare cardiac anomaly. As far as we are aware the only other heart in which this anomaly has been recognized is the one reported in a recent paper by Grant.[7] In this paper he also mentions what may be another case of this anomaly in a malformed heart described by Mann,[16] but there is no reference to it in the latter's text. Grant[7] was able to trace connections between these spaces and the coronary arteries and presumably with coronary veins. We have been able in our case to trace their connections between branches of the coronary artery and the cavities of the left auricular appendage and ventricle (Figs. 6 A to E).

The embryology and physiology of the intertrabecular spaces have been investigated by Lewis[15] and most recently by Grant.[6] Very early in embryonic development (in rabbit embryos 8.5 mm. in length) the myocardium of the auricle is seen to be pierced by outgrowths from the endothelial lining of the auricle which form capillary spaces between the muscle and epicardium. Similar outgrowths later appear from the ventricle forming epicardial capillaries which are extensions from previously existing intertrabecular

spaces or sinusoids of the ventricles. Grant[6] states that in embryos 17 to 20 mm. the intertrabecular spaces are observed as wide spaces between the growing muscle bundles, but their continuation into the compact myocardium cannot be distinguished from the fine ramifications of the veins and arteries there and all three structures together appear as a capillary network in that region. As the outer portion of the myocardium becomes more compact these spaces are practically obliterated, so that in older embryos they are best seen in the inner spongy portion of the myocardium. It seems to be quite generally agreed that the sinusoidal circulation is replaced by the coronary circulation. According to Lewis[15] further development is marked by a continuous growth of the arteries and veins and by a regression of the intertrabecular spaces: the muscle columns coming together reduce many of the spaces to strands of endothelium without lumen. Grant[6] has been unable to satisfy himself that actual obliteration takes place. According to him the outermost intertrabecular spaces are narrowed down by the compact myocardium to capillary tubes which are joined by coronary vessels extending inward from the epicardium. The capillaries arising from the central and inner intertrabecular spaces retain their connections with the ventricles. The ventricular communications persist in the adult as the Thebesian vessels of the ventricle.

It is difficult to explain here definitely the persistence in growth and the existence of the intertrabecular spaces which normally become reduced to capillaries. It is suggested that a high intraventricular pressure as a result of the cardiac anomaly, occurring at the time of the appearance of the sinusoids, led to a marked increase in their size. Another possibility to be considered is that the persistence and the marked development of the sinusoidal circulation was compensatory to hypoplasia of the coronary arterial circulation brought about by the atresia of the aorta.

Summary. Congenital heart disease in an infant is reported which presents a number of unusual and rare anomalies. These were: Atresia of the Aorta, Hypoplasia of the Left Ventricle with marked thickening of its wall, Hypertrophy, Premature Closure of Foramen Ovale, Dilatation of Right Auricle and Ventricle, Diminutive Left Auricle, and Fibrosis of the Myocardium of the Left Ventricle.

This case presented in addition a very rare anomaly: the Remains of the Sinusoids of the embryonic heart.

The incidence, theories of the origin of these anomalies and the resulting disturbances of the fetal circulation are discussed.

NOTE.—The authors wish to express their thanks to Dr. David L. Farley for permitting us to study and report this case.

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THE INCIDENCE OF THROMBO-ANGIITIS OBLITERANS IN BROTHERS.

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There are certain characteristics of thrombo-angiitis obliterans which are unique in that they are never encountered in other diseases. For instance, one of the mysteries of this ailment is its predominance in the male sex. Its predilection for Russian Jews

is also unique. Up to the present, no adequate explanation of this distribution of thrombo-angiitis obliterans has been advanced. I wish to call attention in the present communication to another unusual characteristic of this disease which has not heretofore been described in the literature nor in the textbooks on the subject.

Family Abstracts. In the examination of over 500 cases of thrombo-angiitis obliterans I have observed 3 families in which it occurred in brothers. In none of these families has there been any history of the disease in parents or grandparents on the maternal or paternal side, nor has there been evidence of the disease in other blood relatives.

Family 1. In the first family I shall describe, 3 brothers are affected with thrombo-angiitis obliterans. The parents of these young men were born in Austria and were apparently free from any evidence of peripheral arterial disease. As far as could be determined, there was no history of this disease in the grandparents or other blood relatives. The 3 young men were born in Austria and came to America in early childhood.

The oldest of the group is 34 and exhibits the mildest form of the disease. His previous history is negative. He began to smoke at the age of 14 and consumed approximately 30 cigarettes a day up to the present. He first noticed symptoms at the age of 33 when, after walking long distances, he began to experience pains in the calf of the left leg of such severity as to necessitate rest before walking could be resumed. There were no other symptoms. Upon examination the left foot was found to be colder than the right and the left dorsalis pedis pulse could not be felt. There was moderate plantar ischemia[1] of the left foot and the oscillometer indicated a slight diminution of pulsation in the left foot. Over the right external malleolus there was a tender, cordlike, red area about 6 cm. in length which had the typical appearance of the superficial migrating phlebitis characteristic of this disease. The upper extremities were normal.

The younger brother, age 33, shows a more advanced stage of the disease. His previous history was negative and his symptoms started at the age of 24 with numbness of the left leg. Shortly after the onset there was noticed the typical migrating phlebitis on various parts of the left leg. Difficulty in walking was soon experienced, followed by severe pain in the left big toe. His condition had become steadily worse so that at the time of examination he could walk only three blocks and then was forced to rest because of a cramp in the right calf and a slight pain in the left leg. About a year ago he noticed recurrence of the migrating phlebitis but on this occasion it appeared on the right arm and since its disappearance the right hand is constantly cold and numb. Upon examination the right foot was found to be colder than the left. No pulses were felt in either foot and there was intense plantar ischemia of both feet, more marked in the left. Oscillometric index at the right ankle was 0, and the left ankle was 0.25. Both radial pulses were present, but upon elevation of both hands a cadaveric pallor developed in the right. The oscillometric index in the hands was 0.5 in the left, 0 in the right. There were no ulcerations nor signs of gangrene. There was intense rubor in both feet in the dependent position, more intense in the right. The nails of both feet were markedly atrophic.

The youngest brother, aged 29 years began to smoke at the age of 17 and has smoked about 15 cigarettes a day since then. His illness started with a typical superficial migrating phlebitis of both legs at the age of 24. The phlebitis disappeared after a few weeks and the patient felt well for about 2 years. He then began to experience pain in the sole of the left foot on walking. This condition has grown steadily worse, so that at the time of my examination he was hardly able to walk at all, and for the past

2 weeks had noticed a small black spot on the lateral aspect of the left big toe. There were no symptoms in the upper extremities. Upon examination the left foot was found to be colder than the right. Plantar ischemia was noted in both feet, more intense in the left. No pulses were felt in the left foot and the dorsalis pedis pulse was absent in the right foot. The oscillometric index at the right ankle was 1.5, left ankle 0. On the lateral aspect of the left big toe near the nail margin there was a bluish discoloration of the skin which, after a few days, became gangrenous and formed a small ulcer, which healed up after a few weeks of treatment.

It is interesting to note in this family the occurrence of migrating phlebitis in each case, also the onset of symptoms in the 2 brothers at the age of 24. In each instance smoking had been started at an early age and was continued for many years.

Family 2. Another family in which 3 brothers were affected with thrombo-angiitis obliterans was of Russian Jewish nationality. All of these were born in Russia and came to America at an early age. The oldest had been treated for thrombo-angiitis obliterans for a number of years in various hospitals throughout the city, where the diagnosis was definitely established. He did not develop gangrene, but at the age of 42 died suddenly, probably due to a coronary artery lesion.

Another brother died at the early age of 35 in a similar manner, probably as a result of cardiac involvement. He had been treated for thrombo-angiitis obliterans by some of the leading specialists in the city.

The third brother, who is now being treated by me for massive gangrene of the left foot, is now 40 years of age and has an advanced degree of thrombo-angiitis obliterans in both lower extremities. A few years ago he also had attacks of precordial distress and dyspnea which were diagnosed as coronary seizures.

All 3 brothers were heavy cigarette smokers. The parents and grandparents had no symptoms of circulatory disturbances of the extremities as far as could be determined.

Family 3. The third family in which I have observed the occurrence of thrombo-angiitis obliterans originated in Austria. The two members of the family who were affected with thrombo-angiitis obliterans were, however, born in America.

The oldest, aged 48 years, had one leg amputated at the age of 30 for gangrene due to thrombo-angiitis obliterans. The other leg was recently amputated in a southern hospital for the same cause.

His brother, aged 43 years, has an advanced case of thrombo-angiitis obliterans with massive gangrene of the left foot. There is also moderate involvement of the right foot. Both patients are heavy cigarette smokers. There is no history of circulatory diseases in the extremities of the parents or grandparents as far as could be determined.

Summary. The etiology of thrombo-angiitis obliterans is still unknown. There are, however, certain peculiarities in the disease which may have some bearing upon the underlying cause: (1) Its predominance in Jews: (2) its predilection for young males; (3) its association with cigarette smokers; (4) its occasional occurrence in brothers with no direct evidence of inheritance.

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ERYTHROMELALGIA AND OTHER DISTURBANCES OF THE EXTREMITIES ACCOMPANIED BY VASODILATATION AND BURNING.

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In 1872 Weir Mitchell[3] reported the case of a sailor who had a hitherto undescribed vasomotor condition of the feet. In 1878 he reported 5 additional cases. The characteristics were as follows: (1) There were attacks of bilateral or symmetric burning pain in the hands or feet; (2) the attacks were initiated or aggravated by standing, exercise or exposure to heat; (3) relief was obtained by elevation and exposure to cold; (4) during the attacks the affected parts were flushed and congested, and exhibited increased local heat; (5) the condition was refractory to treatment. These five basic criteria were postulated as necessary for the diagnosis of this condition. Mitchell applied to the condition the name "erythromelalgia," or "red, painful members." In his second communication he included his observations on 6 cases and 5 reports which he found in the literature. An analysis of the 6 cases Mitchell observed showed that in 3 the condition was bilateral, involving the feet; in 2 it was bilateral, involving the hands; in 1 case, unilateral. In 4 cases the attacks were aggravated or incited by exposure to heat or by exercise, in 4 they were relieved by elevation, in 3 by exposure to cold and concerning 1 case mention of relief was not made. In all there was congestion or engorgement during the attacks. Special mention was made of increased local heat during the attacks in 4 cases; no mention was made concerning 2, but it was implied that this feature was characteristic of all.

In the 5 cases Mitchell derived from the literature, with the exception of Veilpian's, the data were too incomplete to allow of adequate analysis. (Table 1.) Paget's case was not typical, in that cold and exercise produced pallor and numbness in the feet, followed by local heat and redness; this condition suggests a hypersensitive reaction to cold, such as is obtained in chilblains or cold allergy. In Graves' case the condition was not symmetric; one foot was affected at a time, and factors of relief and aggravation were not typical. In Stille's case the hands were livid, hyperesthetic, and there was clubbing of the nails. Although his notes were incomplete, peripheral neuritis is suggested. In the case reported by Greiner there was swelling and pain of the fingers and toes; relief was obtained by application of cold water. There was no evidence of loss of motor and sensory function, and recovery occurred in 3 months. In Case 10, seen by Mitchell himself, involvement was of the right foot, the patient was 82 years of age,

TABLE 1.—ANALYSIS OF CASES REPORTED BY WEIR MITCHELL (1878).

Case.	Age in years and sex.	Regions affected.		Factors in initiating attack.	Means of relief.	Increased local heat or congestion.	Response to treatment.	Comment.
		Feet.	Hands.					
1 . . .	40 M	Both simultaneously	Not stated	Exercise and heat	Elevation and cold	Present	Refractory	
2 . . .	35 M	Both simultaneously	Not stated	Exercise and heat	Elevation and cold	Present	Refractory	
3 . . .	58 M	Both simultaneously	Not stated	Exercise and heat	Elevation	Present	Refractory	Red, tender spots on soles of feet; mucous membranes injected.
4 . . .	29 M	Not stated	Both	Exercise and heat	Elevation and cold	Present	Refractory	Cushions of fingers congested.
5 . . .	.. M	Not stated	Both	Local pressure	Not stated	Present	Not stated	Distribution, blotchy and patchy.
6 . . .	29 F	Not stated	Both	Not stated	Not stated	Present	Not stated	Reported by Stille; generalized redness; clubbed fingers.
7 . . .	22 M	Both simultaneously	Both	Standing	Cold	Present	Recovered in 3 months	Reported by Greiner; muscular and sensory involvement, probably neuritis.
8 . . .	35 F	Both simultaneously	Not stated	Exercise and heat	Cold	Present	Refractory	Reported by Veilpian; numbness of parts.
9 . . .	16 F	One at a time	Not stated	Neither exercise nor heat	Cold	Present	Refractory	Reported by Graves, 1864; cyclic pain with spontaneous remission.
10 . . .	82 F	Right only	Not stated	Not stated	Not stated	Present	Responded to treatment for gout	Cerebral accident; severe continuous pain and swelling of right foot.
11 . . .	.. M	Both simultaneously	Not stated	Exercise and cold	Not stated	Present	Not stated	Reported by Paget; pallor, followed by redness and increased heat of feet.

and hemiplegia, which involved the left arm and the left leg, had occurred previously. Relief was obtained by means of treatment for gout. It seems impossible to accept these 5 cases as examples of erythromelalgia, and Mitchell was in doubt as to how to classify them. Mitchell also reported 5 cases in which there were painful feet, without redness or swelling, but with typical effects from heat and exercise. These he did not accept as typical examples of the disease, because visible flushing or congestion of the affected parts were absent and they are not included in the tables which accompany this paper.

Critical review of Mitchell's printed material convinces me that he described a clinical entity or syndrome of a primary form, which, to my knowledge, never had been reported previously. In the typical, acceptable cases 5 basic signs or symptoms that he emphasized were present. Mitchell did not accept, as characteristic, cases in which flushing and congestion were absent (his Cases 13 and 14), in spite of the presence of high surface temperatures in the affected parts. This is confusing, since local fever or increase in heat, with burning distress, may be present, without marked flushing or congestion. Phenomena of vasodilatation vary in degree, and the essential factor is increase in temperature rather than redness of the skin.* The important point is whether the surface temperature increases with, and parallels, the burning distress. If this is accepted as a modification of Mitchell's criteria the grouping of cases of erythromelalgia is more comprehensive, and the conception of the syndrome is clarified.

From subsequent reviews of the literature by Cassirer[1] and by May and Hillemand,[2] it is seen that nothing has been added that would allow one to change, to any great extent, the original concept that a vasomotor neurosis exists, as outlined by Mitchell. However, a survey of many of the cases in the literature makes clear that the original concepts of the disease have been lost sight of, and many and varied forms of vascular disturbance have been erroneously classified as examples of erythromelalgia. A review of the literature for the last 10 years reveals only 1 case that conforms to the criteria necessary for the diagnosis of erythromelalgia. The majority of the reported cases indicate the tendency to employ the term erythromelalgia to describe a symptom; for instance, erythromelalgia is spoken of as occurring in polycythemia vera, when the reporter means a secondary disturbance arising from vasodilatation. The term erythromelalgia is, strictly speaking, not accurately descriptive, and has led to confusion and mistakes in

* From more modern studies we have learned that increased local heat indicates dilatation of the arterioles, and redness, dilatation of surface capillaries and venules. These are not necessarily parallel; in fact, more often are disassociated than otherwise. Following sympathetic ganglionectomy the feet become hot, but redness of the skin is absent. Conversely, in the cold, red extremities of thromboangiitis obliterans there is arteriolar constriction and dilatation of capillaries and venules.

diagnosis, as a survey of the literature will show. Redness and pain of the feet are present in other conditions, as well as in erythromelalgia; for instance, in thromboangiitis obliterans, in localized arteriosclerotic disease when the feet are in the dependent position, in gout, in cellulitis of low grade involving the feet or hands and in certain cases of Raynaud's disease in the stage of recovery or overreaction, in which the hands or feet become excessively hot and red. A more correctly descriptive name should embrace the concept of increase in local heat, or vasodilatation. Redness, flushing, or local congestion may vary widely or may be absent in the presence of arteriolar dilatation and hot extremities. In my grouping of cases I have followed this more concise interpretation of the disturbance.

The pathologic basis of erythromelalgia has not been established. Many and diverse changes in the peripheral nerves and vessels, and in the spinal cord have been described, none of which, however, leads to the belief that any characteristic lesion has been discovered.

Material and Methods of Study. A series of patients, whose major complaint was burning in the feet or hands, was hospitalized for study, thus minimizing the effects of changing environmental temperature. The purposes were: (1) To determine the relationship, if any, of the burning distress to the surface temperature of the affected part; (2) to study the variations in surface temperature and local symptoms in relation to posture, exercise and exposure to heat and cold; (3) in a small group of cases, by the method of inducing fever by injection of foreign proteins, to determine the thresholds for perception of the burning sensation in relation to surface temperature regions in which the burning was felt; (4) in 4 cases in which burning distress of a paresthetic type was present, associated with some degree of vasodilatation, by inducing spinal anesthesia to the point of total analgesia in the feet, to determine whether or not the pain could be relieved, and thus to obtain important information as to the origin of the pain, whether it was peripheral or central.

Eighty-one cases were studied, in all of which burning pain of the hands or feet was a prominent or disabling symptom. The following groupings were made: Group 1 included 10 cases which represented, I believe, true primary erythromelalgia. This gives an incidence of approximately 1 of every 200 cases of peripheral vascular disease seen at The Mayo Clinic. Group 2 was composed of 3 cases of primary unilateral disturbance of vasodilatation involving either the feet or hands. Group 3 was made up of 23 cases of paresthesia, with some intermittent vasodilatation of the affected part, but in which parallelism could not be demonstrated between the surface temperature and the burning distress. Group 4 included 27 cases of paresthesia, in which burning distress was present, the affected parts were cold, and periods of vasodilatation did not occur. Group 5 was constituted of 10 cases of polycythemia vera, with

bilateral or unilateral disturbances of vasodilatation of the extremities, in which the burning distress was the major symptom. Group 6 included 8 cases which could not be classified.

In addition, there was a number of cases of Raynaud's disease, in which, during periods of warm weather or under exposure to increased degrees of environmental temperature, the excessive amount of vasodilatation in the hands and feet frequently constituted rather severe distress. None of these cases was included in this study, because the underlying disturbance was clearly a vasospastic rather than a vasodilator condition. In this report will be presented the data on the cases in Groups 1 and 2.

Study of Group 1: Erythromelalgia. All cases except Case 3 (Table 2) exhibited four of the five basic signs and symptoms described by Mitchell. I have ceased to consider nonamenability to treatment as an essential characteristic. Localized flushing usually was present in some degree during the attacks, but that the sharp degree of vasodilatation was more decisive was evident by palpation and was proved by the rise in surface temperature, or by the marked increase in elimination of heat, as determined by the calorimeter. With subsidence of the attack there was a sharp drop in the temperature of the parts. In all cases the disturbance was bilateral either in the hands or feet, and in all the peripheral arteries were patent. The distress was uniformly instigated or sharply aggravated by heat, exercise or standing; relief was obtained by elevation or by local or general application of cold. In the more severe cases local congestion, pulsation in the veins and localized hyperhidrosis and hyperesthesia were observed during the stage of hyperemia. In none was any associated disease present, and the vasomotor condition apparently was primary. In Case 3 the effects of heat and cold were not present, and the disturbance was not always bilateral, but in other respects the observations were so definite that inclusion of the case was thought justifiable.

Case Reports. CASE 1.—A man, aged 57 years, whose case was the most severe in this entire series, exhibited in every respect the characteristic phenomena described by Mitchell. The bilateral attacks of burning of the feet had been present for 22 years. At first the condition had been intermittent, and complete relief had been obtained with rest, cold and elevation, but within a few years before the patient was seen at the clinic it had progressed to such a degree that almost complete and continuous disability was present. In the summer months, to obtain relief, he had lived on the banks of a river and had spent the days walking about on the wet sands. Wearing shoes or covering the feet had caused most excruciating pain. During the attacks marked congestion and increased local heat were present. At the clinic many and varied medical and surgical measures were tried without avail. The patient committed suicide 2 years after he was seen.

CASE 2.—A man, aged 27 years, gave a history of having had attacks of burning pain in the hands and feet for 6 years. He was not completely disabled. Local flushing was mild, but surface temperatures were high

TABLE 2.—SUMMARY OF CASES OF ERYTHROMELALGIA SEEN AT THE MAYO CLINIC.

Case	Age in years and sex.	Severity of attacks.	Parts affected.	Duration of complaint, years.	Bilaterality of condition.	Subjective symptoms.	Exciting factor.			Factor giving relief.			Color of parts during attacks.	Surface temperature of affected area.	Results and subsequent course.
							Hot weather.	Exercise.	Standing.	Elevation.	Cold water.	Rest.			
1	57 M	Definite	Plantar surface and dorsum of feet.	22	Bilateral	Burning, stinging	Yes	Yes	Yes	Yes	Yes	Yes	Flushed	Sharp increase	Suicide 2 years later.
2	27 M	Definite	Distal half of soles of feet; heels; hands	6	Bilateral	Burning	Yes	Yes	Yes	Yes	Yes	Yes	Slightly flushed	Sharp increase	Markedly improved 5 mos. later
3	34 F	Definite	Soles of feet; fleshy parts of hands	4	At times unilateral	Burning	No	Yes	No	No	No	Yes	Slightly flushed	Sharp increase	Essential hypertension; not followed.
4	53 F	Definite	Both feet and hands	Many	Bilateral	Burning	Yes	Yes	No	Yes	Yes	Yes	Flushed	Sharp increase	Not followed.
5	35 F	Definite	Both feet and hands	3	Bilateral	Burning	Yes	Yes	Yes	Yes	Yes	Yes	Flushed	Sharp increase*	Some improvement.
6	55 M	Definite	Feet and great toes	Not noted	Bilateral	Warmth	No	Yes	No	No	No	Yes	Not noted	Increased to 36° C.	Four years later feet about normal.
7	62 M	Definite	Pressure areas of soles of feet	12	Bilateral	Burning pain	Yes	Yes	Yes	Yes	Yes	Yes	Not definite	Marked increase	Practically unchanged 3 years later.
8	54 M	Definite	Feet and legs	10	Bilateral	Burning pain	Yes	Yes	Yes	Yes	Yes	Yes	Red	Increased to 35° C.	Disappeared in 2 years.
9	78 F	Definite	Soles of feet	4	Bilateral	Burning distress	Yes	Yes	Yes	Yes	Yes	Yes	Red	Increased	Not followed.
10	54 M	Definite	Balls of feet and toes	1.5	Bilateral	Excessive burning pain	Yes	Yes	No	Yes	Yes	Yes	Flushed; dilated veins	Marked increase†	Condition much worse in right foot.

* See Table 3.

† See Table 4.

during the attacks. The attacks were usually brought on by exercise, standing and heat, and were accompanied by mild congestion and by pulsations in the veins. At times the attacks were less marked and were not accompanied by definite changes in color. At all times the symptoms were accompanied by sharp increase in surface temperature. Marked pain was usually felt when the temperature of the skin reached about 34° C. (Fig. 1.) The only atypical feature in this case was that, after a period of rest of 5 months, he reported that his condition was markedly ameliorated. I have no evidence that this improvement was complete or permanent.

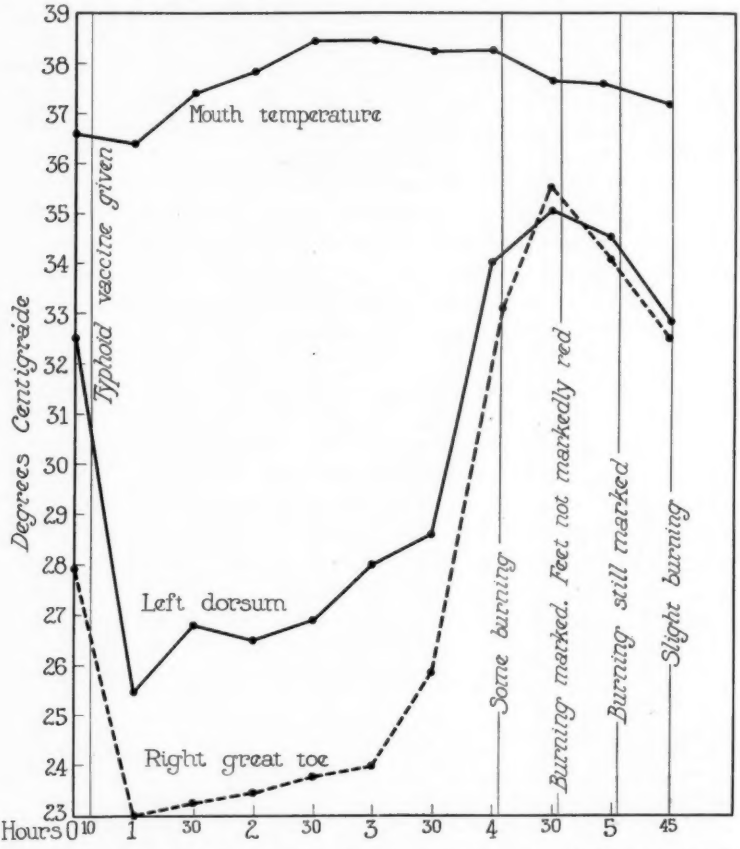

FIG. 1.—(Case 2, Table 2.) Surface temperature of feet in relation to subjective sensation.

CASE 3.—A woman, aged 34 years, with essential hypertension, had attacks of burning pain in the soles of her feet and in the palmar cushions of her fingers and hands. Exercise seemed to be the main exciting factor; hot weather and standing were without definite effects. Likewise, relief was obtained by rest, whereas there was practically no relief from application of cold water and from elevation. During the attacks the involved parts were slightly red and were hot to the touch. The painful areas and increased local heat coincided. Relief from rest was accompanied by a marked drop in local temperature.

CASE 4.—A woman, aged 53 years, with involvement of both hands and feet, had had sensitive feet for many years. This condition had progressed to such a point that when the temperature of the house was more than 70° F. (21° C.) a burning pain developed, accompanied by local congestion and redness of both feet, and associated with a sharp rise in local temperature. She had also noted, within the three months before her registration at the clinic, a similar condition in the hands. The distress was not brought on by standing, but by a moderate amount of exercise, and increase in environmental temperature. Associated with this condition was mild neurosis and nervous exhaustion. The patient was not traced and the subsequent course is unknown.

CASE 5.—A woman, aged 35 years, following a miscarriage 3 years before admission to the clinic, had noted burning and increased heat in the portions of the feet which bear pressure. There were two types of pain—diffuse, superficial burning, and, with further aggravation from exercise, deep, burning pain. There was also increased local heat, mild redness and dilatation of the veins. The hands were also involved to a less degree. There was no sweating during the attacks. The effects of exercise on the surface temperature of the feet are shown in Table 3. Between attacks,

TABLE 3.—EFFECTS OF EXERCISE ON SURFACE TEMPERATURE (DEGREES C.) OF THE FEET.*

	Left foot.		Right foot.		
Time.	Plantar surface, second toe.	Dorsum.	Plantar surface, second toe.	Dorsum.	Comment.
10:45 A.M. . .	28.5	31.4	31.3	31.7	Feet cool and comfortable; no exercise.
11:30 A.M. . .	25.8	30.1	29.3	30.6	At rest; no symptoms.
12:00 NOON . .	25.1	29.5	28.5	30.0	At rest; no symptoms.
3:00 P.M. . .	35.5	35.5	35.9	35.9	Patient walked 13 blocks; feet dry and hot; burning.
4:00 P.M. . .	34.9	35.5	35.3	35.1	At rest; no change in symptoms.
5:00 P.M. . .	33.2	34.1	34.3	34.2	At rest; burning practically disappeared.

* Detail concerning Case 5 of Table 2.

with rest, a difference of 2.8° C. was noted in the surface temperature of the plantar surfaces of the toes of the two feet. Following a brisk walk of thirteen blocks the feet were dry, hot and burning, and the temperature of the left and of the right foot increased to 35.5° and 35.9° C., respectively. With 2 hours' rest the temperature of the left foot had dropped 2.3° and that of the right foot 1.7°, and the burning distress had practically disappeared.

Studies of the effect of posture on the surface temperature disclosed that short periods of elevation produced a decrease of 1° to 2° C. in surface temperature but did not give complete relief. It was found that periods of 30 minutes to an hour were necessary for the temperature to decrease to a point at which burning would disappear. Perception of pain was present when the cutaneous temperature was approximately 33° C.

CASE 6.—To a man, aged 55 years, barometric changes and exercise were the chief factors in producing the burning distress in the feet, whereas rest was the main measure of relief. The effect of atmospheric temperature was not decisive. It seemed necessary to include this case in our series, for during the attacks the surface temperature was as high as 36° C. With a short period of rest the temperature would subside, and the attack was ended. It is possible that some degree of paresthesia, or of progressive,

localized arteriosclerosis may have been present, for subsequent reports from this patient revealed that four years later the condition had largely subsided, and that the feet were giving very little trouble. This case and Case 3 should perhaps be designated as atypical examples of erythromelalgia.

Case 7.—A man, aged 62 years, 12 years before his admission here, had had his feet "frozen." Following this, he had noticed burning and other paresthetic sensations in the areas of both feet that were subjected to pressure. The abnormal feature was the tendency of the distress to be more or less continuous; the congestion and redness were not pronounced. The aggravating effect of heat, exercise and standing were definite, and relief with elevation, cold and rest was decisive. During the periods of excessive pain the surface temperature of the feet was markedly increased, and it was found that it paralleled the burning sensation. The temperature at which pain appeared was about 33° C. The feet were comfortable at reasonable temperatures below 30° C. It was felt that probably some paresthesia was present in this case. Changes were not demonstrable in the peripheral arteries. Treatment was without avail.

Case 8.—A man, aged 54 years, 10 years before his registration here, had noted that after he had been on his feet during the day, or had been exposed to heat or exercise, there was hyperhidrosis and there were blisters on the soles of the feet. In the summer of the following year severe burning pain of the soles of the feet developed, and as it progressed involved the lower parts of the legs. The condition was bilateral and symmetric. Aggravation and relief under certain circumstances were typical. The parts were congested during the attacks. The surface temperature was 35° C. during the night, in a warm room, when his feet were covered with bedclothes, at which time he complained bitterly of the pain. During the time he was free from the distress the temperature of the feet was about 25° C. Roentgenograms of the vessels disclosed some calcification of the arteries of the legs, but normal pulsations were present. Cinchophen, contrast baths and enforced periods of rest were prescribed for him. He was observed a number of times, and the condition gradually disappeared in 2 years. It is questionable whether medical measures had any effect on this.

Case 9.—A woman, aged 78 years, apparently in good general health, for 4 years had had attacks of burning pain in the soles of the feet. She had also noticed small erythematous areas on the soles. These local areas were extremely hot to touch during the attacks. The condition was bilateral, and was brought on by hot weather, walking and standing; relief was obtained by elevation, application of cold and rest. There was no evidence of disease of the arteries of the feet. Roentgenologic examination gave evidence of slight rarefaction and osteoporosis of the bones of both feet. During the periods of distress the surface temperature was sharply increased, but records of exact temperature were not obtained. During the time when she was in comfort the feet were cool to the touch. The condition progressed to a point of almost complete disability. It was felt that the diagnosis of erythromelalgia was justified in this case, but there was also some generalized arteriosclerosis without occlusion, probably compatible with her age. Contrast baths, cinchophen and rest gave slight relief. Her case was not followed.

Case 10.—A man, aged 54 years, 18 months before admission here, without antecedent disturbances in health, noticed burning pain in both feet, more marked in the right. This difficulty was first noticed in the summer and was especially severe when the patient was playing golf. There had been progressive increase in the severity of the condition. Heat and exercise produced the pain, and rest, cold and elevation relieved it. He described the distress as a deep, burning pain localized on the plantar and dorsal

surfaces of the anterior part of the arch and of the toes. During the attacks the surface temperature was high in the painful portions, and there was marked congestion and dilatation of the veins. Of particular interest were the occasional periods of refractiveness to stimulation, which lasted 7 to 10 days following a severe attack. He could exercise freely during these periods of freedom, without pain. Changes were not demonstrated in the peripheral arteries. Observations during the attack (Table 4) disclosed marked congestion of the right foot, and that surface temperatures in the affected portions ranged from 35° to 36° C. There were hyperesthesia and mild sweating. The pain was intense and localized deep in the foot. Oscillometric tracings disclosed marked increase in amplitude of pulsations of arteries (Fig. 2). The left foot reacted to a temperature of 34.4° C., but was less congested, and pain was present only in the first toe. The right foot was elevated; relief of pain followed, and the surface temperatures and pain decreased in parallel degree. When the surface temperature of the right foot dropped below 33° C. (not shown in table) pain almost ceased. The man was of a hypersensitive type.

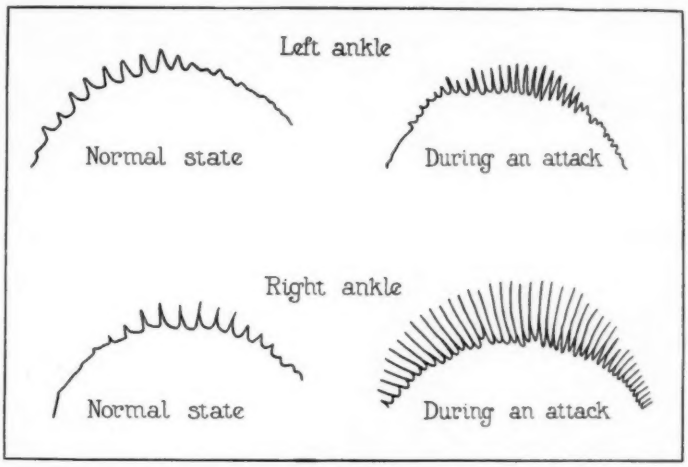

FIG. 2—(Case 10, Table 2.) Oscillometric tracings to demonstrate difference of pulsations in normal state and during attack.

The rate of elimination of heat in the right foot, as measured in the foot calorimeter, during normal periods, was 33 small calories for each minute for the entire foot, or 0.32 small calories for each square inch for each minute (normal range, 0.46 to 1.15). During an attack the loss of heat for the entire foot was 205 calories, or 2.01 calories for each unit area (Fig. 3). This measurement of transference of heat is an indirect measure for volume flow of blood in a unit of time, and the figures obtained in this case indicate a huge increase of more than 600 per cent in flow of blood during the period of vasodilatation.

The studies on the concentration of oxygen in the venous blood of the right foot before and during the attack were also instructive. With the surface temperature measuring 31° C., and no subjective symptoms, the concentration of oxygen was 57 per cent, a normal value. During the phase of active vasodilatation, when the cutaneous temperature was 35.3° C., the concentration of oxygen was 83 per cent. This indicates blood with oxygen content approaching that of arterial blood (94 to 96 per cent). This gives further evidence of the high degree of dilatation of the arterioles.

TABLE 4.—SURFACE TEMPERATURES (DEGREES C.) OF FEET DURING ATTACK.*

Time, A.M.	Right foot. Dorsum.	Right foot. Plantar surface, anterior arch.	Left foot. Dorsum.	Left foot. Plantar surface, anterior arch.	Comment.
	32.2	31.6	31.2	31.4	Patient at rest; comfortable; no pain.
	32.4	31.4	31.2	31.6	Control period.
9:20	..	34.2	..	..	Right foot flushed, graded 1; veins prominent; burning distress just perceptible.
9:25	..	34.9	..	..	Foot covered and at level of body.
9:32	..	36.5	..	..	Subjective feeling of heat and burning pain; increase of subjective burning; veins dilated.
9:45	..	36.7	..	..	Foot felt as if on fire; pain more severe.
9:50	..	36.8	..	..	Throbbing burning pain; face flushed; mild tachycardia; rate 100.
9:55	..	36.4	..	..	Foot hanging down; violent burning pain.
10:00	..	36.1	..	34.4	Right foot elevated; slight subjective relief; left foot in horizontal position.
10:05	..	35.9	..	..	Gradual relief of pain and burning.
10:20	..	35.6	..	35.3	Mild residual burning; burning in left foot.
10:25	..	35.5	..	35.5	Burning slight; moderate pain in left foot.
10:30	..	35.4	..	..	Residual burning in right first toe.

* Details concerning Case 10 of Table 2.

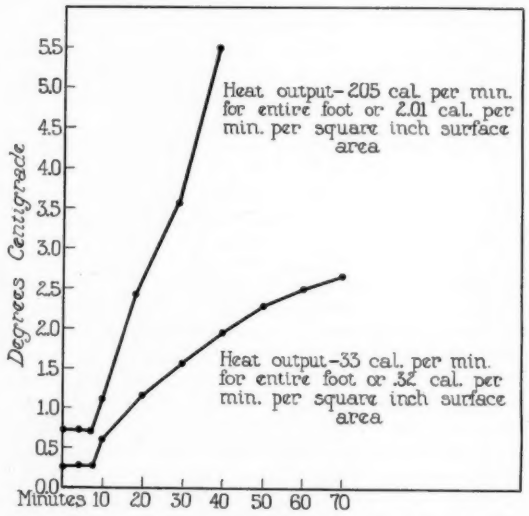

FIG. 3.—(Case 10, Table 2.) Increased limitation of heat during an attack of pain, with great vasodilatation.

Study of Group 2: Unilateral Disturbance in Vasodilatation. This group was composed of 3 cases of disturbance in vasodilatation, 2 of which were typical of erythromelalgia, except that the condition was unilateral. (Table 5.)

TABLE 5.—CASES OF UNILATERAL DISTURBANCE OF VASODILATATION OF THE EXTREMITIES SEEN AT THE MAYO CLINIC.

Case.	Age in years and sex.	Parts affected.	Duration of complaint, years.	Character of attacks.	Subjective symptoms.	Exciting factor.	Factor giving relief.	Color of parts during attacks.	Swelling of parts.	Surface temperature of affected area during attacks.	Pulsation of blood-vessels.	Treatment	Results; subsequent history.
11 . .	46 M	Right foot	20	Definite	Burning pain	Spontaneous	Elevation and walking	Unchanged	None	Right foot 30.1° C.; left foot 27.6° C.	Normal	Contrast baths	Not followed.
12 . .	48 M	Right foot; anterior arch	1	Indefinite	Burning pain	Hot weather and exercise	Elevation	Red at times	None	Right foot almost 1° higher than left	Normal	Rest and cold foot baths	Pain 6 months later.
13 . .	48 M	Palmar surfaces of fingers of left hand and 3.5 years later left foot	2.5	Indefinite	Burning throbbing pain	Hot weather and exercise	Elevation, cold water and partial relief with rest	Purplish red; local sweating	Questionable	Right first finger 27.9° C.; left first finger 34.2° C.	Normal	Radium locally	Complete relief in 3 months; returned 3.5 years later with similar condition of left foot.

CASE 11.—A man, aged 46 years, had attacks that appeared spontaneously during the night, with relief on walking. Thus, the factors of excitement and relief were not typical. However, the patient was included in this series because the symptoms and increase in surface temperature were closely parallel. Apparently the condition was primary, for no causative factors were found.

CASE 12.—A man, aged 48 years, had a characteristic case, except that the symptoms were limited to the right foot. The surface temperatures of the right and of the left foot during periods of rest and during periods of exercise (Fig. 4) show clearly the unilateral nature of the disorder, and that the threshold for burning was approximately 33.5° C. With a drop in

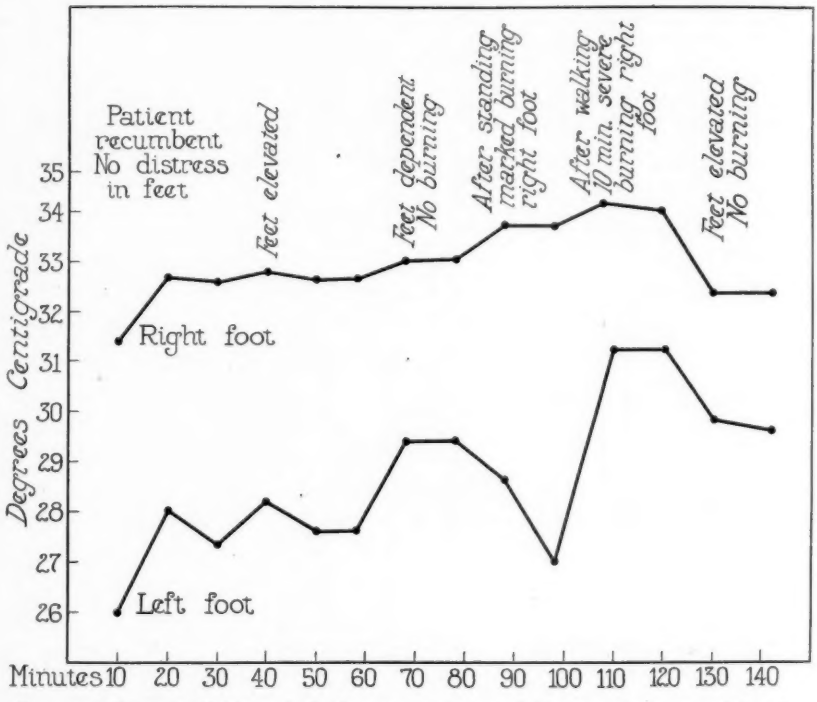

FIG. 4.—(Case 12, Table 5.) Surface temperature of feet in a case of unilateral disturbance of vasodilatation.

temperature of approximately 1° C., the burning was relieved. The response to exercise of surface temperature of the left foot was approximately that obtained in a normal person.

CASE 13.—A farmer, aged 48 years, gave a history of having had a burning sensation in the palmar surfaces of the fingers of the left hand for 2½ years. Objectively, during the attacks the finger pads, and the regions at the bases of the fingers, became intensely red, swollen and congested, with marked increase in the surface temperature. These episodes were brought on by exercise and by hot weather; relief was obtained by elevation, application of cold and rest. The surface temperatures of the palmar surface of the left first finger during the painful attack reached 34.2° C., but in the corresponding region on the right, or unaffected side, the temperature was

27.9° C (Table 6). Hyperhidrosis and hyperesthesia of the affected parts were present during attacks. The condition at times became very distressing and had progressed until it had caused almost complete dis-

TABLE 6.—TEMPERATURE (DEGREES C.) OF RIGHT AND LEFT HANDS IN DISTURBANCE OF VASODILATATION OF LEFT HAND.*

Time, P.M.	Left palmar surface. First finger.	Left palmar surface. Third finger.	Right palmar surface. First finger.	Right palmar surface. Third finger.	Comment.
3:30	34.2	34.1	27.9	29.9	Patient at rest; burning pain in left hand.
4:10	32.9	33.4	26.3	28.7	
4:45	32.6	32.7	24.3	27.7	
5:30	30.9	30.8	22.4	25.7	

* Detail concerning Case 13 of Table 5.

ability. Nothing was found in the examination to indicate any predisposing factor or a primary disease. Six months following local application of radium the patient obtained complete relief. He returned 3½ years later, with a similar condition in the left foot (data not included in Table 5).

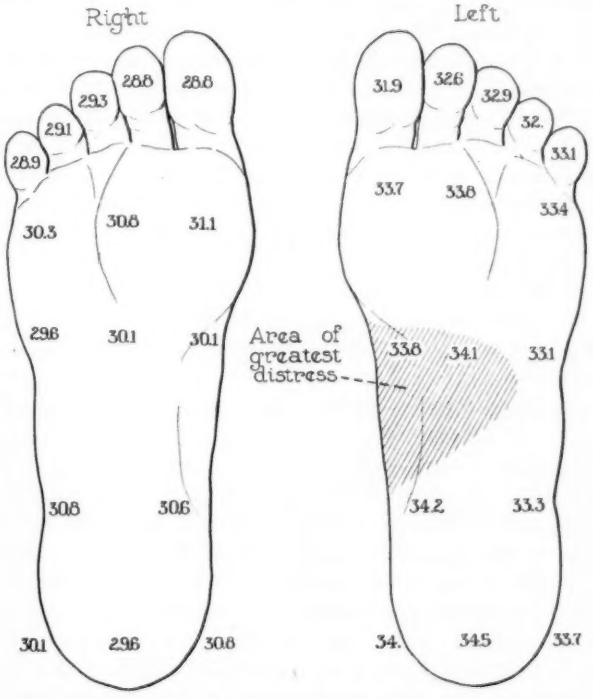

FIG. 5.—(Case 13, Table 5.) Shaded portion indicates painful area. Numerals indicate surface temperature which is evidence of unilateral nature of the disturbance.

This had developed in the preceding year. The attacks were excited by exercise and hot weather, and relief was obtained by elevation and application of cold. The areas of vasodilatation are shown in Fig. 5. Slight

symptoms were present also in the right foot, but they were very mild and practically unnoticed by the patient, unless he was specifically questioned. It will be noted from this figure that the area of greatest distress corresponded rather closely with the greatest increase in surface temperature. Both feet were somewhat congested, the veins were dilated, and if exercise was persisted in the entire foot participated in the "vascular storm." During an attack the output of heat was 42 calories for each minute for the entire foot, whereas elimination of heat from the left foot was exactly half of this. An interesting feature in this case was the evidence of possible early polycythemia vera. The blood volume was 103 cc. for each kilogram of body weight; the percentage of cells by the hematocrit method was 57; the concentration of hemoglobin was 117 per cent, and erythrocytes numbered 5,630,000 per c.mm. The spleen was not palpable, but the appearance of the man's face and mucous membranes suggested early polycythemia vera. Diagnosis cannot be made until time has elapsed. Radium was applied locally, the results of which are not known to date.

There is some question as to whether the 3 cases in this group should be considered to be examples of erythromelalgia. If the condition had been definitely bilateral doubt would not have been raised. That it was unilateral throws grave doubt on the correctness of diagnosing these conditions as erythromelalgia. In my opinion, it would be necessary for complete follow-up study of these patients to be carried out to make certain that no underlying primary disease was present, particularly polycythemia vera, since unilateral vasodilating disturbances have been fairly common in this condition.

General Comment. It is apparent from this study that the syndrome described by Mitchell represents one of the conditions that is most rarely found in clinical medicine. Statistics at The Mayo Clinic indicate that the incidence is approximately 1 case in every 200 cases of peripheral vascular disease, and that the yearly incidence is 1 to 40,000 cases for the total number of patients registered.

It is important to separate from the group of cases of erythromelalgia those cases in which there is burning pain in the hands and feet, secondary to other diseases. The hot, burning disturbances of acral portions, observed in polycythemia vera, may especially be mentioned. This interesting phenomenon of vasodilatation is frequently a precursor, or early symptom, of polycythemia vera, and at times is the only condition of which complaint is made. Similarly, vasodilatation is present in some cases of peripheral neuritis, especially those due to the toxic effects of the heavy metals, such as thallium, mercury and arsenic. Cases of gout are at times confusing; response to rest, heat and exercise make it possible to distinguish erythromelalgia from other conditions.

Greater difficulty is encountered in older subjects who give some evidence of peripheral and general arteriosclerosis, and whose major complaints are of burning extremities. These conditions frequently are bilateral, and symptomatically they conform, in some degree,

to erythromelalgia. The great majority of these cases are examples of paresthesia of central origin. The essential point to determine is whether the subjective symptom of burning is associated with increase in heat of the affected part. I have found that some vasodilatation is often present. It is essential to learn, then, if the increase in surface temperature attains a level of 33° to 36° C., and if this increase, and the return to normal after it, parallel the pregression and regression of the subjective distress. Usually the other paresthetic symptoms, and the factors of atypical relief and aggravation, indicate clearly their paresthetic nature. There is a larger group of older subjects who have burning distress in the feet but who do not give evidence of vasodilatation. A definite point in eliminating this group from consideration as examples of erythromelalgia is the statement by the patient: "While my feet are cold, they burn." This is easily corroborated by determinations of surface temperature made in the periods of distress. Dissociation of burning and surface temperatures is the rule. This condition is designated as burning paresthesia. It usually occurs in older subjects, who give evidence of cerebral and local arteriosclerosis, and after hemiplegia of hemorrhagic or thrombotic origin. Definite information on this point can be obtained by spinal anesthesia; with complete analgesia of the affected parts the burning distress may still persist.

The perception of pain in relation to surface temperature is of interest. This varies within a fairly narrow range, but the increase in temperature does not furnish the sole explanation of the subjective distress. Sensitivity of the patient must play a large part, and intermittency of the periods of vasodilatation is important. Patients who have undergone lumbar ganglionectomy often have surface temperatures of the feet of 33° to 34° C., but subjective burning is rarely present. One patient, following cervicothoracic ganglionectomy for arthritis, had subjective burning in the hands, and relief was obtained by elevation. This condition disappeared in 8 or 10 days. The high surface temperature is fairly constant, and perception of it is dulled. If fluctuations of cutaneous temperature are rapid, and extend over a range as wide as 8° to 10° C., I believe distress would be noted subjectively. If this occurred in a hypersensitive person probably severe pain would be the complaint. An additional unknown fault of the nervous system may be necessary to produce the syndrome.

Bilateral distribution of the objective and subjective manifestations of erythromelalgia is most essential to its identification. However, complete symmetry may be lacking. It was observed in practically all of my cases that in one extremity there was a greater amount of vasodilatation and subjective distress than in the other. This is well shown in Case 10 (Table 2). The complaint was largely of a unilateral condition, but it was found that the dis-

turbance was bilateral, aggravated in the right foot. This variation in the grade of vasodilatation was fairly frequent. There remained 3 patients in whom the disturbance of vasodilatation was distinctly unilateral, both as regards objective evidence and subjective complaints. These cases could not be accepted as examples of erythromelalgia. I am of the opinion that this disturbance of vasodilatation may be a precursory symptom of some other disease.

It is evident that patients who complain of sensations of burning in the extremities offer considerable trouble in diagnosis. Satisfactory nomenclature is lacking. However, I believe accurate studies of surface temperature in relation to subjective distress allow primary separation into two groups: those with and those without local vasodilatation.

This distinction is fundamental: if increased vasodilatation is present, and parallels the degree of pain or distress, and is bilateral and intermittent, I believe the diagnosis of erythromelalgia is warranted, provided primary or associated disease is not present. If these features are present relief by application of cold or by elevation and aggravation by exercise or heat seems necessarily a corollary.

Of special interest is the refractory state that was observed in Case 10 (Table 2). Following a fairly severe attack induced by exercise, for 6 to 10 days an equal or greater amount of exercise would produce slight, if any, vasodilatation. Then, if a period of rest of a few days was given exercise would excite a severe attack. A systemic reaction, consisting of tachycardia and slight flushing of the face, with a sensation of heat, was observed during a severe local reaction in the feet. This observation is most unusual, and may throw some light on the etiologic mechanism of erythromelalgia, suggesting a possible chemical or hormonal agent as a basis for the vasodilatation. An analogy to this is observed in certain cases of cold allergy with systemic reactions.

Since excess volume of flow of blood is the basis of the symptoms in erythromelalgia, gangrene or trophic changes should not ensue. The cases reported in the literature as erythromelalgia with gangrene, I am convinced must be erroneous. They probably represent either cases of thromboangiitis obliterans, with the usual rubor or cases of arteriosclerotic disease, with burning paresthesia.

The treatment of erythromelalgia is still unsatisfactory. Two of the cases which I have seen recently responded well to application of radium locally, and I believe this should be tried in all cases. However, these patients have not been observed for a sufficiently long period to allow me to be certain of the lasting effect of this treatment. In the cases of long standing some degree of mental deterioration may develop, due largely, I believe, to the unending annoyance and distress incident to the disease.

Summary and Conclusions. Erythromelalgia, first described by Weir Mitchell, is a vasomotor disturbance of unknown etiology and is an extremely rare disease. The term erythromelalgia is not entirely accurate, since redness and pain in the extremities are common to several vascular diseases of diverse types. In erythromelalgia attacks of local vasodilatation, with increased local heat and pain, constitute the basic disturbance.

Four fundamental criteria are essential to diagnosis of the disease: (1) Bilateral burning pain in the extremities; (2) sharp increase of local heat in the affected parts, but redness, flushing or congestion may vary in degree; (3) production and aggravation of the distress by heat and exercise, and (4) relief by rest, cold and elevation.

During the attacks the temperature of the affected parts should be found to reach or exceed 33° or 34° C. and pain usually becomes evident when this temperature is reached or exceeded. Augmentation in arterial pulsation and in the rate of loss of heat give further evidence of the high degree of dilatation of arteries.

Certain methods of study to distinguish between the different conditions in which burning extremities occur are outlined.

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THE BLOOD PRESSURE IN THE ARTERIES OF THE EXTREMITIES IN NORMAL SUBJECTS AND IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE.

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In the study of the abnormal physiologic changes resulting from vascular diseases of the extremity the blood pressure is an important factor, for in any hydrodynamic system, flow is a function of pressure and cross-sectional area. It is apparent that the frequent involvement of the vessels of the lower extremities makes it desir-

FIG. 1.—The cuffs for recording the blood pressure in the dorsalis pedis and posterior tibial arteries applied to the limb and attached to the sphygmomanometer. The lowest cuff is for the dorsalis pedis, the middle one is for the posterior tibial and the upper one is a "shut off" cuff.

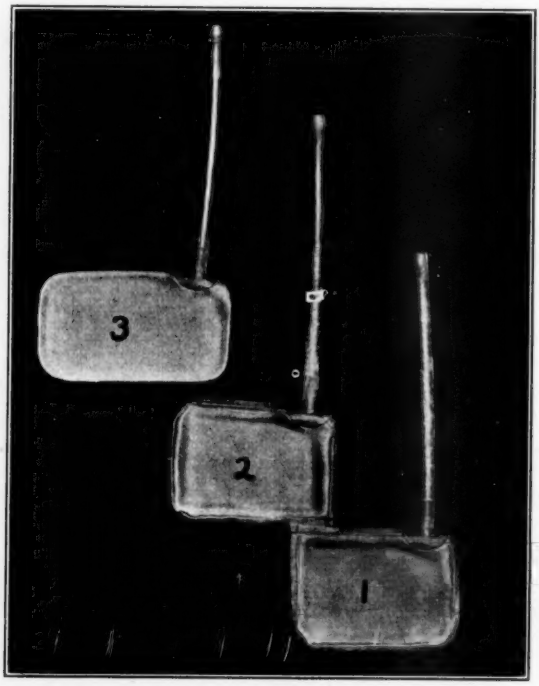

FIG. 2.—The arrangement of the special cuffs: No. 1, dorsalis pedis; No. 2, posterior tibial; No. 3, "shut off." Although No. 1 and No. 2 are attached there is no communication between them.

able to obtain data on the pressure changes in this location but no apparatus has heretofore been available for such measurements. With the development of a reliable recording sphygmomanometer* it was thought to be possible, by using special cuffs, to obtain the pressure in the dorsalis pedis and posterior tibial arteries (Fig. 1). These cuffs were made† (Fig. 2) and were found to give a satisfactory record of the blood pressure in these vessels. It was then decided to study, not only the changes with arterial disease, but also the alterations in pressure brought about by changes in posture in normal adults.

It is well known that in the presence of occlusive vascular disease elevation of the extremity results in pallor and ischemia, while dependency of the structure causes rubor and cyanosis and this has been assumed to be a hydrostatic effect. In order to determine the changes in arterial pressure with alteration in position, 16 normal adults were studied. After a period of rest in the horizontal position, the pressure in the brachial, dorsalis pedis and posterior tibial arteries was determined. That of the latter 2 vessels was then recorded, first in elevation at an angle of 45 degrees and then in dependency with the limb hanging over the edge of the table. The results are shown in Table 1 from which it is seen that the average pressure in the brachial artery is midway between the pressure in the posterior tibial and dorsalis pedis, that of the former being consistently higher, while the latter is at a lower level. This is shown in Fig. 3. The effect of alteration in position may also be noted from this table and is shown in Fig. 4. If the lower extremity is elevated at an angle of 45 degrees the average fall in pressure in the posterior tibial artery is found to be 46 mm. Hg. The average height of elevation above the horizontal was 660 mm. and computation of the hydrostatic effect shows a theoretical change of 51.3 mm. Hg., which gives a difference from the recorded change of 5.3 mm. Hg. The dependency of the limb at an angle of 90 degrees caused an average rise of pressure in the posterior tibial artery of 28 mm. Hg. The average amount of depression below the horizontal was 390 mm. which would give a hydrostatic effect of 30.3 mm. Hg. and hence a difference of 2.3 mm. Hg. from the recorded result. A typical record of the change in pressure with a shift in position is shown in Fig. 5.

The same correlation between the theoretical and actual results of alteration in position is found in the case of the dorsalis pedis artery. In this vessel an average elevation of 680 mm. gives a fall in pressure of 39 mm. Hg., while the calculated hydrostatic effect is 52 mm. Hg., and an average depression of 410 mm. gives a rise of pressure of 37 mm. Hg. with a calculated change of 32 mm. Hg.

* Tycos recording sphygmomanometer.

† We are indebted to Mr. Samuel Amdursky of the Taylor Instrument Companies for his assistance in obtaining the desired apparatus.

TABLE 1.—THE READINGS OF THE BRACHIAL BLOOD PRESSURE AND OF THE POSTERIOR TIBIAL AND DORSALIS PEDIS BLOOD PRESSURE IN THE HORIZONTAL, ELEVATED AND DEPENDENT POSITIONS IN NORMAL ADULTS.

	Brachial.		Posterior tibial.								Dorsalis pedis.							
	Flat.		Down.			Flat.		Up.			Down.			Flat.		Up.		
Subject.	Syst.	Diast.	Syst.	Diast.	Dist. mm.	Syst.	Diast.	Syst.	Diast.	Dist. mm.	Syst.	Diast.	Dist. mm.	Syst.	Diast.	Syst.	Diast.	Dist. mm.
1	114	62	172	110	420	148	85	92	55	640	154	80	400	110	56	50	?	730
2	124	77	162	107	460	135	78	110	?	730	...	...	...	No	pulse			
3	112	65	205	110	370	158	82	110	40	620	180	100	450	105	45	80	?	740
4	128	78	160	112	?	112	72	50	25	?	130	80	?	112	60	No	pulse	
5	140	90	170	130	340	147	80	97	40	660	125	60	340	107	60	75	45	660
6	112	70	157	75	400	122	74	72	30	620	137	87	480	115	58	50	?	620
7	137	75	165	90	430	147	80	90	47	770	150	74	430	126	68	84	46	770
8	122	75	132	82	400	105	70	No	pulse	650	...	...	...	No	pulse			
9	142	85	218	130	340	187	110	125	40	610	197	?	410	160	90	95	45	610
10	110	70	155	97	360	128	76	78	42	720	124	65	420	88	55	No	pulse	720
11	140	94	145	95	380	130	78	93	40	620	140	90	380	112	75	80	?	620
12	112	78	170	110	410	122	75	65	35	690	...	...	...	No	pulse			
13	122	73	218	148	?	170	108	108	45	?	...	...	...	No	pulse			
14	157	95	...	...	...	158	90	105	50	650	165	100	420	122	70	72	30	640
15	122	80	158	110	340	157	100	122	64	620	160	90	420	105	60	92	50	730
16	120	76	143	90	440	114	73	90	60	670	...	...	...	No	pulse			
Average	126	78	168	106	390	140	83	94	44	660	151	83	410	114	63	75	43	680

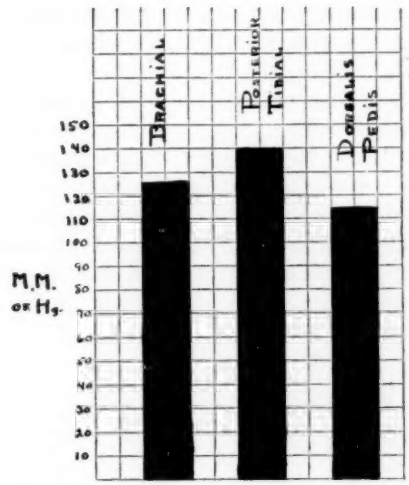

FIG. 3.—The normal relation of the systolic blood pressure in the horizontal position at rest in the brachial, posterior tibial and dorsalis pedis arteries.

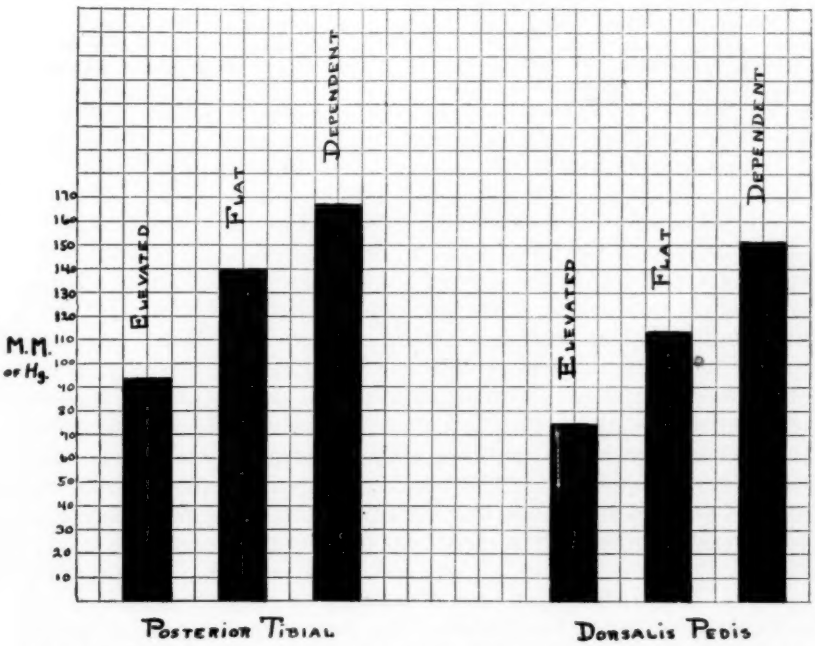

FIG. 4.—The average change in systolic blood pressure due to alteration in position of the limb.

The results recorded with the dorsalis pedis artery are probably not entirely accurate because the weak character of its pulse, particularly with the limb elevated, made interpretation of the records difficult.

If simultaneous readings are taken on the pressure in the brachial and posterior tibial arteries it is noticed that with elevation of the limb and consequent fall in pressure in the vessels of the extremity there was a slight rise in the pressure of the brachial artery. It is possible that the elevation of the limb reduced the volume flow through the extremity and hence increased the blood volume in the general circulation. The converse of this effect is noted with depression of the extremity.

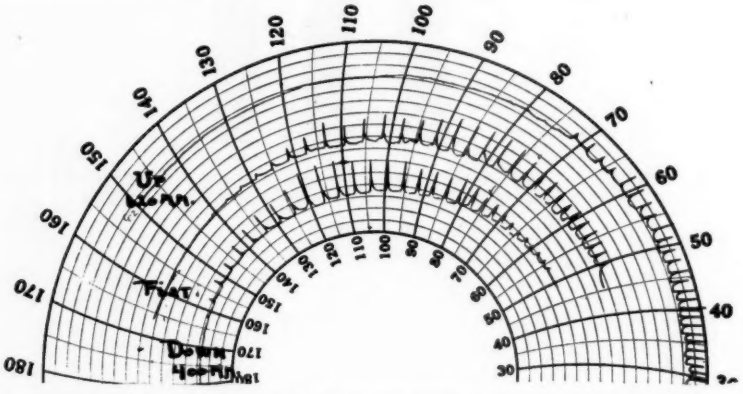

FIG. 5.—A typical chart of the effect on the blood pressure and amplitude of the pulse wave in the posterior tibial artery of elevating and depressing the limb.

The instrument used has the advantage of giving not only a permanent record of the blood pressure in the vessel being studied but also gives a chart of the strength of the arterial pulsation. This latter effect is the same as the oscillometric determination with the Pachon instrument and is of equal importance. When applied to the dorsalis pedis and posterior tibial arteries it serves to give an index of the caliber of these vessels. In normal subjects it was observed that if the pulsation in one of these vessels was vigorous that in the other was often weak. It most frequently occurred that the posterior tibial had the stronger pulsation and occasionally it was found to be impossible to record the pulse in the dorsalis pedis artery. It appears that a reciprocal relation exists between these vessels.

It was hoped that by means of a sensitive instrument, pressure could be recorded in the posterior tibial and dorsalis pedis arteries even in the absence of a perceptible pulse. It is well known that blood flow occurs in a vessel in which no pulse can be detected. However, this was found to be impossible and no record could be

obtained if the perceptible pulsation of the peripheral vessels was absent. On the other hand, it was found that by using the arm cuff applied to the leg a record of the intravascular pressure and amplitude of the pulse could be recorded for the larger vessels. The study of the force of the pulse wave in these arteries gives a record of the oscillometric effect and may be used to determine the level and degree of involvement in cases of thrombotic or sclerotic occlusion. An illustration of this is shown in Fig. 6 which is a tracing from a case of diabetic endarteritis with a pregangrenous lesion. It will be seen that the force of the pulse just above the knee (popliteal artery) is good, while just below the knee (tibial and peroneal arteries) it is nearly absent. This shows that the level of

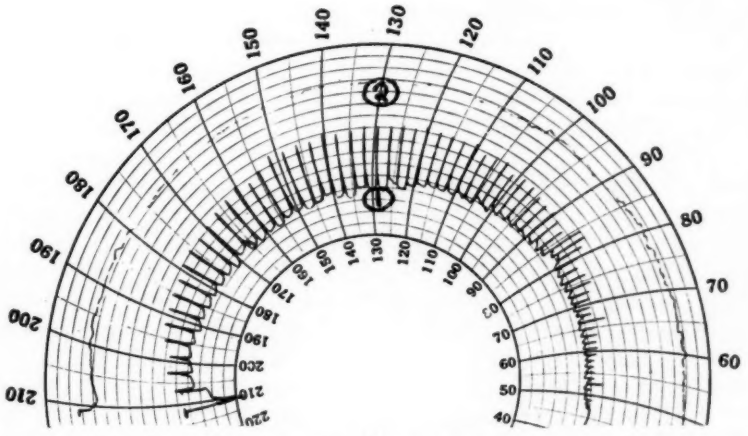

FIG. 6.—Diabetic endarteritis with abrupt arterial occlusion. The popliteal artery (1) just above the knee has a strong pulse while there is no pulse; (2) 3 inches lower at the level of the tibial tubercle. Subsequent dissection showed the obstruction at the bifurcation of the popliteal artery into its posterior tibial and peroneal branches.

occlusion is near the bifurcation of the popliteal artery and that the vessel above this point is not seriously involved. Subsequent dissection confirmed this finding. The use of the intrument to obtain a record of the character and amplitude of the pulse in patients with arterial disease of the extremities gives concrete information that is of value in deciding upon the therapy to be used. Various types of involvement are found varying from gradual progressive occlusion (Fig. 7) down the leg to sudden, sharp level of thrombotic obliteration.

Discussion. The data presented show that a change in posture of the lower extremities materially alters the blood pressure in the arteries of the limb. Change of position also influences the strength of the pulsation of the vessel. When the leg is in the dependent position, the systolic and diastolic pressures increase and the pulsa-

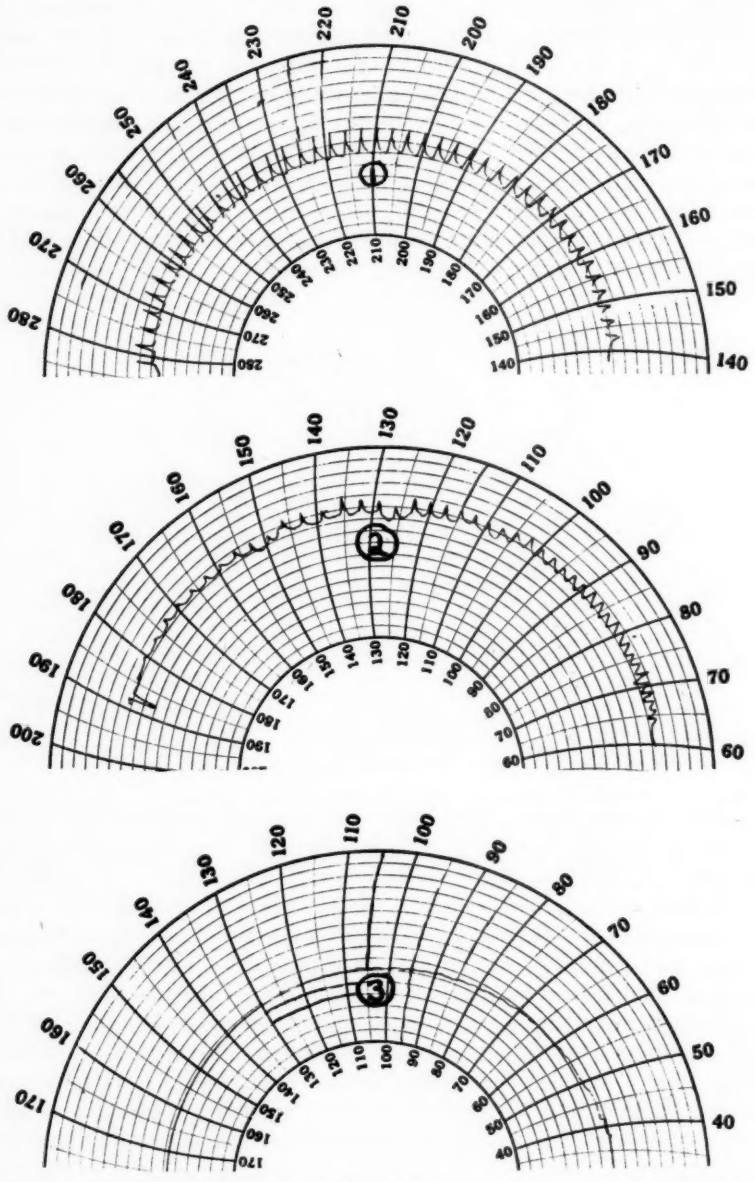

FIG. 7.—Gradual arterial occlusion from arteriosclerosis: 1, shows a good pulse below the knee; 2, shows a diminished pulse at midcalf, and 3, shows an absent pulse at the ankle. The posterior tibial and dorsalis pedis pulses were imperceptible.

tion is maximal. Elevation of the limb gives the opposite effect, namely to decrease the blood pressure and diminish the force of the pulse. This result gives a mechanical explanation of the phenomena observed with change in position of a limb afflicted with severe arterial disease. Under such conditions, an important part of the physical examination is the observation of the effect of posture on the circulation of the part. It is found that elevation results in blanching, pallor and even a cadaveric appearance. This ischemia is produced at a definite angle in each individual depending upon the amount of arterial involvement and Buerger[2] has defined this as the angle of vascular sufficiency. Samuels[7] has shown that motion of the toes accelerates this phenomena and may in addition produce symptoms resembling intermittent claudication. Matas[4] has made use of the circulatory changes accompanying shift of position to evaluate the level of efficiency of the collateral circulation. It is obvious that if the blood pressure and force of the pulse are diminished in normal subjects by elevating the limb, then under conditions of impaired circulation there is apt to be complete incompetence in this position and ischemia will result.

The depression of the limb, with its consequent increase in blood pressure and force of the pulse, allows more blood to be forced through the narrowed channels. It has been shown[5] that in the later stages of obliterate endarteritis the vasomotor control and vasomotor gradient in the lower extremities is obliterated. Thus, there will be no counteracting mechanism for the increased pressure of the hydrostatic effect and cyanosis and rubor will result. Turner, Newton and Haynes[9] have recently demonstrated an increase in the blood content of the legs held in dependency.

In the management of patients with peripheral vascular insufficiency this effect of position on the circulation should be considered. If the circulation is incompetent the limb should never be elevated except during brief intervals for the purpose of exercise. It would appear to be beneficial slightly to depress the leg thus increasing the intravascular pressure but this should never be done to the extent of causing rubor or cyanosis since edema may result.

Little need be said of the use of the instrument for determining the force of the pulse wave in subjects with vascular disease. This method is exactly similar to oscillometry with the Pachon[6] instrument and Samuels[7] has discussed the value of oscillometry in these conditions. Recently Simpson[8] has compared the Pachon and Tycos machines in a variety of vascular disturbances. We have used the Pachon instrument for a number of years and we feel that with the recording sphygmomanometer, there is not only the advantage of having permanent calibrated records but also that this instrument is more sensitive and gives more reliable readings than does the Pachon. Burdick *et al.*[3] have recorded the differences in blood pressure in the arm and leg of normal subjects and have

shown that the femoral pressure is consistently higher than that of the brachial. Our observations show that this difference extends to the posterior tibial artery as well. The explanation of this phenomena is given by Bazett[1] to be the conversion of kinetic energy into stress.

It is expected that the further use of the apparatus described will not only aid in obtaining accurate information about cases of arterial disease but also will serve to advance our knowledge of peripheral vascular physiology.

Summary and Conclusions. 1. The effect of alteration in position of a limb on the blood pressure of the peripheral arteries has been studied. It was found that elevation of the extremity lowered the blood pressure while its depression raised the intravascular pressure. These results correlated with the theoretical hydrostatic change of such a maneuver.

2. In peripheral vascular lesions it is essential to know the condition of the main arteries as well as that of the arteriolar and subpapillary branches. The vasoconstrictor influence upon the latter structures is demonstrated by a skin temperature response to known agents. The state of the main vessels can only be determined by estimation of the perceptible pulse or by oscillometry.

3. In the past the Pachon instrument has been the standard for oscillometric determinations. The Tycos recording sphygmomanometer has the advantage of giving an accurate, permanent calibrated record for this purpose.

4. The use of this instrument with the special cuffs devised is considered desirable to determine not only the condition of the vessels in disease but also to study vascular physiology.

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CORONARY DISEASE IN 100 AUTOPSIED DIABETICS.

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Since the discovery of insulin the clinical picture of diabetes has been changing. While in the preinsulin era malnutrition, infection, acidosis and coma were the chief problems and dangers of the diabetic, we now find that vascular disease is playing a greater part, while coma is becoming more and more infrequent. This is well brought out by the statistics of Joslin,[1] in an analysis of 1756 diabetic deaths. It will be noted that since the introduction of insulin the deaths from vascular disease have increased from 28 to 47 per cent. In a more recent series of 42 diabetic deaths reported by Joslin,[2] in 1928, not a single death was due to coma and about one-half died of vascular diseases.

It is a familiar fact that the peripheral arteries of the diabetic are prone to sclerosis. Attention was drawn to this early, because of the frequency of peripheral gangrene in diabetes and the presence of sclerotic vessels in amputations for gangrene. More recently the clinical detection of peripheral arteriosclerosis has been made even more exact by the use of the Roentgen ray method. Aside from the peripheral arteries, comparatively little attention has been given to changes in other vessels.

Warren and Root[3] found in 17 autopsies on diabetics above the age of 40 years 5 cases with no coronary sclerosis, 4 with slight change and 8 with marked coronary disease and myocardial degeneration. Vascular disease apparently was more frequent in the obese. Wilder,[4] in 58 autopsies at all ages, found 34 per cent showing extensive coronary disease. In 75 per cent of the cases with peripheral gangrene a high degree of coronary sclerosis was noted. Bowen and Koenig[5] recently published an excellent report on the study of the peripheral arteries in the diabetic by means of the Roentgen ray. Incidently, they presented a table of 18 cases from a series examined, in 1924, who had died since that time. Of these 18 cases 7 died cardiac deaths, 5 of these presenting the characteristic clinical features of coronary thrombosis.

In the present study the records of 100 diabetics that came to autopsy were analyzed with special reference to the cardiovascular pathology. The coronary arteries were considered as diseased only when there was marked sclerosis with definite narrowing and partial obliteration of the lumen of one or more large branches, for it is this type which has definite clinical significance. The essential data are summarized in Tables 1, 2, 3 and 4 and Chart I.

Discussion of Tables. Table 1: In this table the incidence of coronary disease by decades is presented. It is to be noted that whereas the frequency is low in the earlier decades, there is a sharp rise above the age of fifty years. Of 26 autopsies below this age there are but 2 instances of coronary disease, or 7.7 per cent. Of the 74 autopsies above the age of fifty years coronary disease was present in 39 cases, or 52.7 per cent. This high incidence of coronary sclerosis is in fairly close agreement with the above mentioned report of Warren and Root. These observers, in 17 diabetic autopsies above the age of 40 years, found 47 per cent showing extensive coronary disease. Wilder, in 58 autopsies at all ages, found an incidence of 34 per cent, as compared with 41 per cent in the present series of 100 autopsies. Hepburn and Graham[6] studied the electrocardiograms of 123 clinical cases of diabetes at all ages. Electrocardiographic abnormalities were present in 45.5 per cent, which for the most part were characteristic of coronary disease.

Table 1.—Coronary Disease in Diabetes.

Age.	Autopsies, 100.	Coronary sclerosis. No. of cases, 41.	Coronary sclerosis. Per cent, 41.
10 to 20	1	0	0
20 to 30	2	0	0
30 to 40	11	1	9.0
40 to 50	12	1	8.0
50 to 60	27	14	52.0
60 to 70	33	17	52.0
70 to 80	12	6	50.0
80 to 90	2	2	100.0
Above age of 50	74	39	52.7

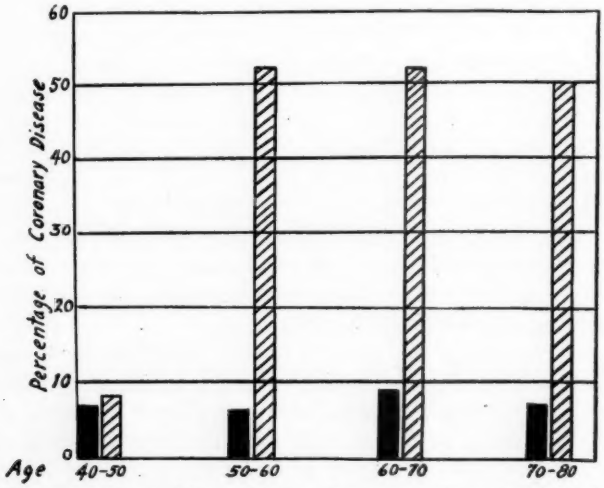

Chart I.—Comparison of the incidence of coronary disease in diabetics and nondiabetics. Shaded columns, diabetics; solid columns, nondiabetics.

Since in any series of autopsies above the age of fifty years coronary disease is not an infrequent finding, it seemed necessary to compare the incidence of coronary sclerosis in autopsies on diabetics with that in general autopsy material. Of 249 consecutive autopsies above the age of fifty years there were 21, or 8.2 per cent, showing extensive coronary sclerosis as compared with 52.7 per cent in the diabetic series of 100 autopsies. The difference in the two groups is thus very striking, indicating that above the age of fifty years the incidence of coronary disease is approximately six and a half times greater in diabetics than in nondiabetics. Chart I shows graphically the comparative frequency of coronary disease in diabetics and nondiabetics by decades.

Table 2: This table shows the distribution of the cases of coronary disease according to sex. It will be noted that there is a preponderance of males, the ratio of males to females being 1.8 to 1. In a previous analysis[7] of 113 cases of coronary disease in nondiabetics that came to necropsy the proportion of males to females was 3 to 1. The greater susceptibility of the male to arterial disease, and especially coronary sclerosis, is well known. There is an indication that in diabetes the tendency to coronary arterial change is almost as great in the female as in the male. This is true not only of the coronary arteries but even more so for the peripheral vessels. Of 21 instances of peripheral gangrene there were 12 females and 9 males. This series is too small to draw definite conclusions, but it suggests that the comparative resistance of the female to the development of arterial disease is distinctly lessened when diabetes is present.

TABLE 2.—SEX DISTRIBUTION OF CORONARY DISEASE IN DIABETICS.

		Coronary sclerosis.	
	Autopsies.	No. of cases.	Per cent.
Males	57	29	50.9
Females	43	12	28.0

Table 3: The weight of the heart was recorded in 98 of the cases. Although no exact figure of heart weight can be given as the upper limit of normal, it is probable, according to Bell and Clawson,[8] that the normal weight seldom exceeds 400 gm. in the female and 450 gm. in the male. When a heart weight above these limits is not associated with such conditions as valvular disease, adherent pericardium, syphilitic aortitis, chronic glomerulonephritis and hyperthroidism, it may be assumed with few exceptions that primary hypertension was present in life. Using 450 gm. as the upper limit, 17 of the 98 cases, or 17.3 per cent, showed evidence of hypertrophy. In 2 instances there was an explanation in the heart for hypertrophy, in 1 case an old rheumatic mitral lesion, in the other a luetic aortitis. There were 86 autopsies above the age of 40 years and 15 cases of idiopathic hypertrophy occurred above

this age, giving an incidence of 17.8 per cent. Bell and Clawson,[8] using otherwise unexplained cardiac hypertrophy at autopsy as evidence of hypertension, found that 13.3 per cent of males and 10.9 per cent of females over 40 years of age had primary hypertension. Using this criterion, there is indication that hypertension is but slightly more frequent in the diabetic than in the general population. Opinion has been divided regarding the blood pressure in diabetes. It has frequently been stated that diabetes is a cause of hypertension. The observations of Major[9] indicate that hypertension is not a prominent feature even in the elderly diabetic. This is in agreement with the conclusions which may be drawn from a study of the heart weights in Table 3. It is noteworthy that of the 15 cases of hypertrophy 12, or 80 per cent, showed extensive coronary disease. Bell and Clawson emphasize the frequent association of coronary lesions and hypertensive heart disease. They found severe coronary disease in approximately 40 per cent of necropsies showing hypertensive heart above the age of 50 years. This indicates that coronary disease is twice as frequent in the hypertensive with diabetes as in the uncomplicated hypertensive heart.

TABLE 3.—WEIGHT OF HEART IN 98 AUTOPSIES ON DIABETICS.

	Heart weight.	
Grams.	Coronary.	Noncoronary.
100 to 199	0	1
200 to 299	3	25
300 to 399	8	21
400 to 499	20	8
500 to 599	9	2
600 to 699	1	0
Below 450 grams	29	52
Above 450 grams	12	5

Coronary Disease and Peripheral Gangrene. Of the 100 autopsies, gangrene of the lower extremities of a mild or severe degree was present in 21 instances. There were 12 females and 9 males in this group. They were distributed according to age as follows: 1 between 40 and 50 years, 7 between 50 and 60 years, 10 between 6 and 70 years and 3 between 70 and 80 years. Of the 21 autopsies showing peripheral gangrene severe coronary disease with occlusion was present in 13, or 62 per cent. Wilder,[4] from a study of 58 autopsies, found a high degree of coronary sclerosis in 75 per cent of diabetics with gangrene. It is important that the frequency of this association should be recognized. The probability of cardiac involvement should be taken into account, since surgical treatment is frequently considered in the diabetic with gangrene. This should add weight in the direction of conservative treatment and emphasize the study and care of the heart when more radical measures are necessary.

Aside from coronary disease there was little other cardiac change in the 100 autopsies. There were 3 cases of hypertrophy characteristic of hypertension heart with slight sclerosis but patent coronary vessels. All 3 died of congestive failure. There was 1 case of lues of the aortic orifice with aortic regurgitation. There was 1 instance of chronic rheumatic mitral valve defect. That there is a striking infrequency of rheumatic valvular disease in diabetes is emphasized by Joslin.[10] He states that up to 1917 he could recall no case of diabetes under 50 years of age in which the patient complained of shortness of breath or presented the signs of an incompetent heart due to valvular disease of a definite and unquestionable rheumatic origin. Later several such cases did come under his observation. In a series of 56 autopsies upon diabetics at the Deaconess Hospital there was but 1 case of rheumatic heart disease. In reviewing the histories of diabetics, on the other hand, rheumatic fever is not uncommon. Barach[11] noted an incidence of 16 per cent in 226 cases. However, in 37 diabetics with a past history of rheumatic fever there occurred but 1 case of valvular heart disease. This indicates a definitely reduced incidence of cardiac involvement, since ordinarily it is estimated that rheumatic fever is followed in approximately 40 per cent of the cases by chronic valvular disease. Barach concludes that when a potential diabetic suffers an attack of rheumatic fever the heart is relatively immune to involvement. Joslin suggests the explanation that few children or young adults with severe rheumatic heart disease live through the 25 or 35 years that are necessary to bring them to the age when diabetes is common.

Another type of pathologic change which occurred in this series was a pale, swollen and cloudy heart muscle, the picture of a toxic myocardium. This was present in practically every case in which death was due to acidosis and coma. Foster,[12] in studying the pathologic changes in diabetes, noted myocardial degeneration at necropsy in every case of coma. This suggests the possibility that the circulatory insufficiency which occurs in diabetic coma may in part be due to this toxic myocardial change.

The exact mode of death could not be determined in every case of coronary disease, but in 35 the manner of death was quite definite. The causes of death in these 35 cases were as follows: A cardiac death occurred in 18, of which 11 were congestive heart failure and 7 anginal. The 17 noncardiac deaths were due to the following causes: gangrene, 7; cerebral accident, 4; coma, 1; pneumonia, 1; cellulitis, 1; mesenteric thrombosis, 1; accidental, 1; suicide, 1. In none of this latter group were there any clinical features indicative of heart disease. It is evident that coronary disease must be suspected in the diabetic even though a clinical picture of heart disease is absent.

Comment. There is no generally accepted explanation for the prevalence of arteriosclerosis in diabetics. Joslin[1] believes that the

arteriosclerosis is secondary to the diabetes and that the duration of the disease is an important factor. He has found that diabetes of 5 years' duration or longer is practically always accompanied by some degree of arterial change. Joslin strongly favors the theory that the cholesterol which is usually increased in the diabetic's blood is the basis for the vascular change. He is influenced in this by the work of Aschoff, who believes that an increased amount of cholesterol in the blood is one of the prerequisites for arteriosclerosis. The sclerotic change follows a fatty deposition on the arterial walls, especially at points subject to mechanical strain. As support for his views Aschoff points to the many feeding experiments in rabbits, in which prolonged administration of cholesterol has almost uniformly been followed by typical changes in the aorta. Although this theory seems to apply to the conditions which exist in diabetes, there is little or no evidence at the present time that such a process actually takes place.

A different explanation for the association of arteriosclerosis and diabetes is that the diabetes is a result of a generalized arteriosclerosis which also involves the pancreas. The elderly diabetic has frequently been termed the arteriosclerotic diabetic, implying that the arterial disease is the primary process. This theory suggests itself because of the fact that severe arterial disease in diabetes occurs almost entirely at an age period when arteriosclerotic changes are frequent. It cannot be denied that difficulties arise when we attempt to determine etiologic relationships for arteriosclerosis at a period of life when the normal individual is subject to vascular changes. However, there are several studies in young diabetes at age periods when sclerotic changes are ordinarily infrequent, which indicate a high incidence and early development of vascular change. Allbutt,[13] discussing the relationship between diabetics and arteriosclerosis, states that "a plausible suggestion is that the glycosuria might be a result of arteriosclerosis in particular areas as, for example, the pancreas." He continues, however, with the statement that this conception occurred to him before he had an opportunity of witnessing the gradual advance of vascular changes as a sequel to diabetes in young persons. Allbutt noted many instances of thickened arteries in children and comparatively young adults, one of the youngest being a girl, aged 14 years.

Joslin,[14] in a study of 52 autopsies, found an incidence of arteriosclerosis of 20 per cent in the second decade and of 59 per cent in the third decade. He mentions a boy whose diabetes began at 10.5 and ended 5.5 years later. The atheromatous plaques in his aorta were plainly evident and not at all to be confused with the minor alterations which occur normally at puberty. Joslin[15] also cites the results of the roentgenologic studies made upon 324 of his diabetics by Morrison and Bogan. Roentgen ray evidence of arteriosclerosis was found in 30 per cent when diabetes began between the ages of

20 and 29 years and in 45 per cent when the onset was between 30 and 39 years. Using the same method in nondiabetics, Bowen[5] noted an incidence of 0.5 per cent in these age periods. More recently Shepardson,[16] also using the Roentgen ray, studied 50 diabetics who were under 40 years of age and in whom the disease had been present for at least 5 years. The average age of the entire group was 23.4 years and 36 per cent showed evidence of vascular sclerosis. This high incidence of arteriosclerosis in the young diabetic indicates that the vascular lesion is an accompaniment of the diabetes gradually increasing in degree with the progress of the disease. Although this does not necessarily mean that the diabetes is the cause of the arteriosclerosis, the evidence is strongly against the conception that the diabetes is secondary to the vascular disease.

Bowen studied the development of arteriosclerosis by means of the Roentgen ray over a period of 3 and 4 years in a group of diabetics who were properly treated and also a group in whom the disease was not well controlled. He describes a greater tendency toward increase in degree of arteriosclerosis in the poorly treated cases. Bowen concludes that the development of severe vascular disease requires several years of neglect of the diabetes. This may explain the relatively low incidence of severe vascular pathology in early life. In the young individual neglected diabetes is rarely of long duration, as there is usually an early fatal outcome. In the elderly the disease is typically mild and frequently symptomless, so that it may go on for a long period without proper treatment and thus lead to the development of extensive vascular disease. A high degree of vascular disease may be found in the young individual if he survives for a period of 10 years or more. This is illustrated in the following case, which has been reported in detail by Dr. Karl Anderson.[17] A white male died at the age of 33 years of cardiac decompensation. Diabetes had been present for 14 years. At autopsy the heart weighed 440 gm. The descending branch of the left coronary artery showed marked sclerosis, the lumen being almost obliterated in places. The right coronary showed extensive thickening but was less involved and there was also a thrombus in this vessel. The pancreas appeared normal and the vessels did not show extensive sclerosis. The renal arteries were severely involved and the lumina markedly reduced. The abdominal aorta showed extensive intimal thickening with several ulcerated areas. Further evidence against the conception of the vascular pathology as the primary process is that in practically every instance in this series of autopsies the history of diabetes preceded the manifestations of the vascular disease by a variable period of time. Joslin,[18] in discussing a group of 122 cases of angina pectoris associated with diabetes, states that the onset of the diabetes distinctly preceded that of the angina in 106.

At the present time it does not seem justifiable to conclude that diabetes is the causative factor in the arteriosclerosis, as no mechanism for this process has been satisfactorily proved. However, there appears to be sufficient evidence that the vascular disease either occurs coincidental with or as a sequel to the diabetes.

Conclusion. 1. An analysis of 100 autopsies upon diabetics shows an incidence of 41 per cent of severe coronary disease. Above the age of 50 years the incidence is 52.7 per cent as compared with 8 per cent in an even larger series of nondiabetics of the same age.

2. The frequency of coronary disease is almost as high in the female as the male.

3. The incidence of hypertensive hypertrophy of the heart indicates that hypertension is only slightly more frequent in the diabetic than the nondiabetic.

4. In diabetics with gangrene the incidence of coronary disease is higher than in the uncomplicated cases.

5. The essential cardiac lesion of diabetes is coronary sclerosis. Other types of cardiac disease are of relatively rare occurrence.

6. The etiologic relationship between diabetes and arteriosclerosis is discussed.

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DIABETIC GANGRENE: INCIDENCE AND PATHOGENESIS: AN ANALYSIS OF 58 CASES AMONG 1008 DIABETICS.*

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The association of gangrene with diabetes was first mentioned by Marchal (de Calvi[1]) in 1852. Since then numerous contributions have appeared in the literature. That gangrene may develop in diabetics is a well-known fact. Various types of gangrene may be found in this group of individuals. The arteriosclerotic form is quite common; obliterative endarteritis is less commonly found; embolic gangrene and thromboangiitis obliterans are relatively rare. There has been considerable discussion as to the status of what has been termed diabetic gangrene. Is there a form of gangrene with sufficient characteristics and clinical findings to warrant a diagnosis of diabetic gangrene thereby establishing its entity? Many authorities insist that one cannot definitely say upon examination of a section of the involved artery whether it is or is not due to a diabetic condition. In other words, their contention is that the arterial lesions are so closely related with the findings in arteriosclerotic gangrene that they can make no distinction between them, concluding therefrom that in diabetes what some term diabetic gangrene is really arteriosclerotic gangrene. Buerger,[2] Beard,[3] and others have taken this attitude. Whether or not they are justified in discouraging the acceptance of diabetic gangrene as a separate form remains to be seen.

On the other hand, McKittrick and Root,[4] Warren,[5] and others have called attention to certain facts and clinical findings which are apt to exist in certain cases of gangrene in diabetics. These findings appear so regularly in this group of cases that even if the microscope does not establish a distinctive form, surely there may be enough evidence clinically to warrant a diagnosis of diabetic gangrene.

The following description of what may be termed diabetic gangrene is usually met with in this group of cases. Although occurring in the aged, it may make its appearance in the fifth decade. Its onset is usually insidious. An unrecognized cellulitis or osteomyelitis of the smaller bones in the foot is frequently responsible for the gangrene. Pain need not be a prominent symptom and sometimes its absence is a striking phenomenon despite the extensiveness of the lesion. Infection, suppuration and sloughing are commonly present. When ulcers develop from the gangrenous processes of the soft

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parts, they may show marked undermining of the edges and an extensive sloughing of the tissues that could not be appreciated by external examination alone. The arteries may not show the pathologic changes that one meets in arteriosclerotic gangrene. This holds true for some cases where despite extensive involvement of a gangrenous process, the dorsalis pedis artery may have a normal pulse and the roentgenographic examination may fail to reveal calcific deposits in the walls of the vessels. Thrombophlebitis is frequently found. The gangrene does not seem to conform to the dry form expected in arteriosclerotic type, rather, it is of the moist variety. It may extend laterally and involve contiguous structures, whereas in arteriosclerotic gangrene there usually is mummification of a toe and if there is extension it is apt to be limited to an area supplied by the same vessel.

For the sake of convenience the clinical facts which may aid in distinguishing between the two types of gangrene are presented in tabular form:

TABLE 1.—SHOWING POINTS OF DIFFERENTIAL DIAGNOSIS BETWEEN DIABETIC AND SCLEROTIC GANGRENE.

	Arteriosclerotic.	Diabetic.
Age	Senile, usually in 7th decade	May occur in 5th or 6th decade.
Pain	Usually severe even with small area of gangrene	Varies; may be absent or mild in early stages.
Infection	Not present	Nearly always present; may have considerable sloughing.
Type of gangrene	Dry	May be dry, but more commonly moist.
Line of demarcation	Present	Often absent.
Extension	Along lines of arterial supply	May extend laterally as well.
Pulse	Absent or markedly diminished	May be present in some cases.
Roentgen ray	Calcification of walls of arteries	Arteries may show no demonstrable pathology.
Pathologic findings	Thickening of the walls with calcific deposits	Atheromatous changes with thrombosis; calcification may or may not be present.
Microscopic appearance of vessels	Medial form of sclerosis	Intimal form of sclerosis.

Incidence of Gangrene in Diabetes. Any attempt to arrange statistical data concerning the frequency of gangrene in diabetes meets with difficulties. The following points arise: First, the period over which the records were accumulated is important. One invariably finds a higher percentage of cases of gangrene in the recent years than preceding periods for obvious reasons. In the later periods, insulin has preserved more patients from the earlier complications, the disease is generally being more efficiently handled and we are now more acutely aware of gangrene than ever before.

Second, the source of the records, whether from office practice, outpatient departments or from hospitals is to be considered. The data collected from patients in institutions will show a higher rate of incidence because as a rule those patients with complications and the severer forms of diabetes are more likely to seek hospital aid. A fairly large number of milder forms of diabetes will not or cannot go to the hospital. This will keep the number of cases of diabetes in hospitals at a lower level and will apparently result in a higher percentage of gangrene. This need not necessarily apply to all hospitals. I have in mind as an exception the New England Deaconess Hospital where Joslin's statistics have been gathered.

The third difficulty is the question as to what constitutes a case of gangrene. One may see a patient with circulatory disturbances with discoloration of a toe or two, but the process does not eventually materialize into gangrene. On the other hand, a diabetic may have circulatory disturbances with marked symptoms and only one or two small spots of gangrene. There may be still a third group with definite evidences of deficient circulation but no apparent signs of destruction of the tissues.

With these facts in mind, the author suggests that all cases showing circulatory disturbances of the extremities be classified in three groups:

GROUP 1. *Gangrene.* Diabetics who have unmistakable signs of gangrene. As a rule, the lower extremities are involved, either the toes, heel or soft parts of the legs. Other areas such as the lungs, buttocks, nose and genitalia may be involved, but they are comparatively rare and have not been included in the author's statistics. This group embraces the various forms of gangrene: the arteriosclerotic, embolic, thromboangiitis obliterans and the so-called diabetic gangrene.

GROUP 2. *Impending or Threatened Gangrene.* Where patients present not only signs of impaired circulation but also definite evidences of trophic disturbances, which have progressed to such a degree that they almost develop gangrene. The typical case is one in which there is a deep seated infection in the foot with swelling and there is encroachment upon the blood supply to the toes by pressure. Usually one finds a purplish discoloration of one or more toes, with coldness of the distal parts. There may be an ominous discoloration of the adjacent tissues. However, in time these signs subside and gangrene is averted. In this class may be included the trophic ulcers which in time may lead to gangrene.

GROUP 3. *Potential Gangrene.* The third group is suggested for those diabetics who have symptoms or signs of deficient circulation. Evidences of an altered circulation may be recognized by the presence of lesions: red spots, scars, scarlike depressions and blebs or by the various methods of studying the circulation, particularly the oscillometer, reaction of the skin to histamin inoculations and

Roentgen ray. The above lesions[6] and descriptions of these methods[7] of investigating the circulation have been described in previous publications.

Analysis of Records. Analysis of 1008 cases of diabetes was made in an effort to see what can be learned in reference to circulatory disturbances as a complication in this disease. These records cover a period of 11 years: 1920 to 1930. The patients were studied chiefly in office practice and the outpatient department. A small number were observed in institutions.

TABLE 2.—SHOWING STATISTICS OF 1008 CASES OF DIABETES MELLITUS WITH REFERENCE TO INCIDENCE OF GANGRENE AND CIRCULATORY DISTURBANCES.

Period.	Total No. cases.	Number of cases of gangrene.		Percentage.
1920–1930	1008	Group I: Gangrene . . .	58	5.75
		Group II: Threatened . .	28	2.77
		Group III: Potential . . .	89	8.82
		Total cases with circulatory disturbances	175	17.3
(*a*) 1920–1925	345	Group I: Gangrene . . .	13	3.8
		Group II: Threatened . .	7	2.03
		Group III: Potential . . .	24	6.95
		Total cases with circulatory disturbances	44	12.75
(*b*) 1926–1930	663	Group I: Gangrene . . .	45	6.78
		Group II: Threatened . .	21	3.16
		Group III: Potential . . .	65	9.80
		Total cases with circulatory disturbances	131	19.75

A glance at the above table shows that 58 cases of gangrene were observed in the entire series of 1008 cases of diabetes, giving a percentage of 5.75. If the threatened cases are included with those of actual gangrene, the percentage would be increased to 8.53 and if all the 3 groups are taken collectively, the incidence of circulatory disturbances in diabetics would rise to 17.3 per cent, or practically 1 patient out of every 6 has evidences of circulatory disturbances and 1 out of every 17 to 18 diabetics has developed gangrene. This is based on the group from 1920 to 1930. The incidence of the various groups of complications is somewhat higher if we confine ourselves to the recent 5-year-period from 1926 to 1930. It is plausible to assume that this percentage indicates more accurately the tendency for the development of complications. During this 5-year-period, 663 cases were observed; 45 patients developed gangrene (6.78 per cent); there were 21 cases of impending gangrene (3.16 per cent) and 65 cases of what we may term potential gangrene (9.80 per cent). Collectively, there were 131 patients out of 663 who showed evidences of impaired circulation, with and without gangrene. In other words, 1 out of every 5 patients showed some evidence of arterial disease.

It may be of interest to compare the author's figures with those reported by others. This has been arranged in Table 3.

TABLE 3.—SHOWING THE COMPARATIVE STATISTICS OF GANGRENE AS A COMPLICATION IN DIABETES.

Reported by.	Hospital.	Period.	Total diabetics.	Gangrene.	Percentage.
Blotner and Fitz	Peter Bent Brigham Hospital, Boston	1913–1925	969	69	7.0
McKittrick and Root	New England Deaconess Hospital	1923–1928	4066	163	4.08
Wendt and Peck	Grace Hospital and office, Detroit	1919–1929	1073	113	10.7
Futcher	Johns Hopkins Hospital	1889–1925	1025	49	4.5
Coller and Marsh	University Hospital, Michigan	1921–1925	650	20	3.2
Lemann	New Orleans Hospital and office	1921–1926	471	25	5.3
Paullin (quoted by Lemann	Georgia	1921–1926	560	15	2.65
	Charity Hospital, New Orleans	1921–1926	439	79	18.0
Lemann[8]	Touro Infirmary, New Orleans	1921–1926	201	20	10.0
	Boston City Hospital	1921–1926	967	109	11.2
	Mass. General Hospital	1921–1926	600	58	9.0
	Montreal General Hospital	1921–1926	1016	36	3.5
Mean average		Total diabetics:	12037	756	6.28
Author's	Office and Outpatient	1920–1930	1008	58	5.75

Pathologic Anatomy of Diabetic Gangrene. The appearance of the extremity varies according to the type of gangrene. In the embolic form, the leg is swollen, moist, extensive involvement, with large bleb formation and a foul odor. The gangrene of thromboangiitis obliterans is a slowly developing one with trophic disturbances, intense pain, often associated with recurring thrombophlebitis, occurs earlier in life than the other forms. The veins as well as the arteries are involved. There is extensive occlusion of the vessels, with distinct evidences of inflammation. Adhesions between the vessels and the accompanying nerves are often found. The thrombus in the lumen may show organization and canalization. Sporadic cases occur in diabetes but they are relatively rare and it is questionable whether the diabetes has any influence upon the production of the gangrene. Judging from the rarity of this combination, when it does occur, the probabilities are that the diabetes developed after the thromboangiitis.

ARTERIOSCLEROTIC GANGRENE is easily recognized by the dry mummification of the tissues. There is a sharp line of demarcation. There may be considerable pain especially when there is ulcer formation. Evidences of arteriosclerosis are present. It usually occurs in the seventh decade or in older individuals. The extension of the gangrene is slow. Infection may or may not exist. If infection is superimposed upon the dry gangrene, extension of the gangrenous process may take place rapidly.

DIABETIC GANGRENE, as mentioned above, has certain characteristics which may be briefly summarized, even at the risk of repetition. Its frequent association with or relation to infection; its occurrence in the fifth or sixth as well as the later decades; the tendency to involve soft parts; the moist type of gangrene; absence

of a line of demarcation; absence of evidences of arteriosclerosis such as the persistence of the dorsalis pulse and negative Roentgen ray findings; the tendency to extensive sloughing and the likelihood of recovery without amputation. The arteries macroscopically may be rigid and the lumen may be occluded. The walls of the vessels are thickened. The occlusion of the lumen may be due to proliferation of cells from the intima, atheromatous plaques and calcific material or it may be the result of a secondary thrombosis. Microscopically, Warren[9] emphasizes atheromatous changes of the vessels, particularly of the intimal type. This type can be recognized by "local thickening and hyalin change of the intima with lipoid infiltration, the presence of cholesterol crystals or the presence of calcified deposits. These changes are practically always accompanied by fraying or reduplication of the internal elastic lamina."

The above may and may not be associated with calcific changes of the vessels because gangrene usually appears in diabetes in the decades when arteriosclerosis is likely to develop.

Another observation by Warren[10] is of interest. He noticed that many of the arteries showed "an infiltration, frequently intimal, with polymorphonuclear or more rarely mononuclear leukocytes."

The veins as a rule exhibit no striking pathologic changes. There may be some thickening of the larger veins and some cellular infiltration but nothing that can be attributed to diabetes. They receive only the slightest comment in the various contributions on diabetic gangrene. In his studies on impending gangrene, Bernheim[11] emphasizes the prominence and bulging out of the veins when standing. Others have mentioned thrombophlebitis. Coller and Marsh[12] mention varicose veins in those diabetics with intractable leg ulcers, but were rarely involved in the group with gangrene. In our series of observations, thrombophlebitis was by no means uncommon. However, the presence of thrombophlebitis may be merely incidental and has no influence upon the development of the complications.

Mechanism of Diabetic Gangrene. There are three forces which are at work producing this condition: (1) Diabetes; (2) changes in the arterial system, and (3) infection. Much has been written about the rôle of diabetes in the production of atheromatosis and arteriosclerosis. The hyperglycemia, the increase in lipoids, the hypercholesterolemia, the acidosis, all seem to have some influence, particularly upon the intima, resulting in various pathologic changes. These in turn may develop into a full blown picture of atherosclerosis. Add to this the usual tendency for the appearance of calcific changes in the vessels and we have briefly a picture of what takes place in the arteries of a diabetic past middle life. The consensus of opinion suggests that a period of 5 years of the diabetic condition is usually found in these cases. However, there are exceptions to this rule.

In time there is a gradual encroachment upon the lumen of the vessels. This may be due to a thickening of the walls or may be the result of thrombus formation. However, regardless of the underlying cause, the result is the same and that is a definite impairment of the blood supply to the parts. This deficiency of circulation results in trophic disturbances and lowers the resistance of the tissue to infection. The disturbance of blood supply will depend upon the rapidity with which these pathologic changes take place. If their development is slow, requiring a period of months before occlusion takes place, nature makes up for this deficiency by the establishment of a collateral circulation. In some cases the extent of this collateral blood supply is very striking. In his contribution on the collateral circulation of the extremities, Bernheim[13] has noticed that extensive occlusion of the main branches may be compensated for by the development of a collateral circulation from small insignificant branches.

The patient may be fortunate in having established a collateral circulation which may practically compensate for the lack of blood supply. Complications may be warded off indefinitely, provided this even balance is maintained. These individuals are always potential cases of gangrene. Any added strain upon the circulation, progression of the disease, or infection however slight may alter the balance and gangrene sets in. Sometimes this complication makes its appearance despite all precautions and care.

Infection is an important factor in the development of gangrene. It is almost invariably present in the so-called diabetic gangrene and may be responsible for its development. Sometimes the infection gains entrance through insignificant crevices of a callus or a break in the skin from minor cuts or abrasions such as the trimming of a corn, cutting toe nails or irritation of the skin from ill-fitting shoes. The lowered resistance of the tissues and the deficient blood supply practically invite an infection and when entrance is once gained, extension of the process is a simple matter. In some patients the infection seems to develop from within. Attention has been called to the fact that an osteomyelitis of the metatarsals may exist without any external signs. It can only be detected by careful examination of the feet. The above facts are emphasized because they may be forerunners of a developing gangrene of the involved area and may shut off the blood supply to the toes by the pressure of the induration upon the already weakened arteries. This evidently is the clinical picture seen in those patients with impending gangrene who have deep-seated infections of the feet with discolored toes bordering on gangrene. The outcome depends upon the management of the case. With skillful handling, the infection may be controlled, and gangrene may be avoided in some cases.

Analysis of the Group With Gangrene. The statistics of the diabetics who developed gangrene are arranged in Table 4. From this

table one can learn some information as to the age, duration of the diabetes, and the end results, when obtainable.

AGE. All but 2 developed gangrene when they were past 50 years. The largest numbers occurred in the sixth and seventh decades. This finding is rather general when compared with statistics of others. Joslin[14] reported that the average age at which gangrene developed in his series was 62 years; the youngest at 36 and the oldest at 82 years. The studies of Blotner and Fitz,[15] and Eliason and Wright[16] were similar to the above. While there may be some variation in the percentages of the sixth and seventh decades, the final analysis shows that the vast majority of cases complicated with gangrene occurs in those past 50 years.

SEX. In the author's series of gangrene, there were 37 females and 21 males. These figures differ from those of others. Blotner and Fitz in their series noticed that there were 38 males and 31 females. Similarly, Eliason and Wright mentioned 33 males and 32 females in their group. It is very doubtful whether any influence of sex can be attached to the development of gangrene.

TABLE 4.—SHOWING AGE, SEX, DURATION OF DIABETES AND RESULT OF THE 58 CASES OF GANGRENE.

Age.	Sex.			Years of duration of diabetes.					Result.	
Decades.	No.	M.	F.	1–2	3–4	5–9	10–14	15–20	Died.	Amputation.
40 to 49 .	2	2	0	0	0	2	0	0	2	2
50 to 59 .	20	7	13	3	4	6	3	4	3	6
60 to 69 .	32	12	20	7	6	6	7	6	10	4
70 to 79 .	3	0	3	0	1	1	1	0	0	1
80 . .	1	0	1	0	0	0	0	1	0	1
Total .	58	21	37	10	11	15	11	11	15	14

Duration of Diabetes. A 5-year-period of diabetes is usually noticed in those diabetics who show evidences of arterial changes. This observation has been confirmed by many. One must remember that this applies to changes in the vessels and is particularly applicable to the young.

Lest a false impression be made, it is worth mentioning the fact that gangrene may develop at any time in an aged diabetic. Arteriosclerosis may have already developed before diabetes comes on the scene. The surmise that this individual has an immunity against complications for 5 years is decidedly erroneous. There is no reason whatever why this diabetic may not develop gangrene at any time. Joslin,[17] in his group of gangrene cases, noticed that 38 occurred in those who had diabetes between 1 and 4 years. In the author's series, there were 10 cases with a history of diabetes between 1 and

2 years' duration; 11 cases between 3 and 4 years; 15 cases between 5 and 9 years and 22 cases of gangrene occurred in individuals who had diabetes for 10 to 20 years. Twenty-one cases of gangrene developed in those who had diabetes less than the allotted 5-year-period, a percentage of 36.2. Of this group, 13 of the cases were in the seventh decade.

Results of Gangrene in Diabetics. Gangrene is now recognized as an important factor in the contributory cases of death in diabetes. McKittrick and Root[18] mention gangrene as a contributory cause in 24.2 per cent of the diabetic deaths. Morrison's[19] figures were 23 per cent; Rabinowitch[20] reported 39.1 per cent; Dublin,[21] in a statistical analysis of 3386 deaths from diabetes in 1929 to 1930, mentions the influence of gangrene in 23 per cent of the deaths. In our series of 58 cases of gangrene, 15 died either following operation or where no surgery was attempted, a percentage of 26.

AMPUTATION. In Wendt and Peck's[22] series of gangrene, 25 per cent resulted in amputation. In Joslin's clinic, McKittrick and Root[23] reported 157 operations upon 138 diabetics for lesions of the lower extremities, from January, 1923, to December, 1928. In this group there were 80 amputations for gangrene, 72 major and 8 minor operations.

The author's studies showed that 16 cases out of 58 resulted in amputation of the leg (27 per cent).

PROGNOSIS. The prognosis of the diabetic with gangrene may be considered from two standpoints, the immediate and the remote. The immediate prognosis depends upon the type and degree of the gangrene, plus the added risks of surgical procedure, if this form of treatment is decided upon. Some cases of gangrene develop quickly. Others have a less conspicuous beginning and for a long time may have no serious effects upon the general condition of the patient. This applies particularly to focal gangrene and the arterio-sclerotic types with involvement of a single toe. Regardless of the benignity of a focal area of gangrene, every case should be looked upon as a serious one. They are always uncertain quantities until healing definitely takes place. They are always susceptible to added infection and when infection sets in, the problem is a grave one. Toxemia is the next development and is an important factor upon the ultimate outcome of the case.

Conservative treatment is advisable in the early stages of gangrene. Absolute control of the diabetic condition and local care of the involved part with measures directed toward the improvement of the circulation may control the gangrene. In some cases, particularly the so-called diabetic gangrene with involvement of the soft parts, the result may be extremely favorable. An occasional case may be cured. This form of treatment requires unlimited patience on the part of the physician; the recovery is a gradual and

long drawn-out process, often taxing the patience of the physician. However, when infection appears and begins to spread upward and general symptoms in the form of toxemia are manifested, it is time to act. A short period of observation may be in order to see whether or not the infection is merely a threat and can be controlled. If the toxemia persists and shows a tendency to progress, radical measures seem to be the only course to pursue. It is inadvisable to prolong the period of observation after the infection has spread beyond the foot and involves the leg, with general symptoms such as fever, sweats, weakness and rapid pulse. There is danger of damaging the myocardium to such a degree as to put it beyond repair after amputation has been performed.

The group of gangrene with amputation presents an unusual status when considering prognosis. In the past few years, thanks to insulin and proper medical care, hazards of surgery upon the diabetic have been eliminated. This pertains to major surgery as well as minor procedures. However, this does not apply to the group of amputations in diabetics. The mortality rate in this series is comparatively high. In the series of 69 cases of gangrene reported by Blotner and Fitz, 16 died while in the hospital. Of the 53 patients who were discharged, 42 were followed up and 5 died within $1\frac{1}{2}$ years after they left the hospital, making a total of 21 deaths (30.5 per cent). In McKittrick and Root's studies, there were 14 deaths in the group of 80 gangrenes, giving an average of 17.5 per cent. However, this applies to the period of their stay in the hospital. In the author's series of 58 cases of gangrene, there were 15 deaths, giving a percentage of 26.

The causes of death in most of the above mentioned group of cases were septicemia and bronchopneumonia. Other causes worth mentioning are coronary artery disease and embolism.

The remote prognosis of the diabetic with amputation is by no means favorable. The forces which were responsible for the development of gangrene are still present. True, he may have learned his lesson and will be more careful in the future. Unfortunately the damage to the vessels cannot be undone. The liability of a recurrence is forever present and the necessity for double amputation is by no means rare.

The duration of life after operation in these diabetics is not so easily determined. Joslin in a recent address mentioned a period of 2 years as the average span of life after amputation for gangrene. No doubt, one will meet with patients who have lived longer than this term of years. One patient in the author's series lived for 5 years, another 3 years. However, when one realizes that nearly every diabetic with gangrene fundamentally has arterial disease and that these pathologic changes are general, involving the coronary arteries as well, with toxic phenomena affecting the various vital

structures added to the usual effects of the diabetic condition, is it any wonder that the outlook is a cheerless one?

Summary and Conclusions. Various types of gangrene may occur among diabetics. The arteriosclerotic type and the so-called diabetic gangrene are the most common. Thromboangiitis obliterans and embolic gangrene are less commonly seen.

The advisability of recognizing diabetic gangrene as a definite form is discussed. The fact that a certain number of cases with gangrene present clinical features and pathologic changes in the vessels, plus the fact that it may be of the moist variety, lend support in deciding that we are dealing with a form other than the well accepted arteriosclerotic type of gangrene.

In order to obtain more definite information concerning the frequency of gangrene and the influence of diabetes upon the vessels the various degrees of circulatory deficiency should be evaluated. They may be graded as potential cases of gangrene, impending and actual gangrene, according to the extent of the occlusion.

Analysis of 1008 cases of diabetes mellitus, observed during a period between 1920 and 1930, shows that there were 58 cases of existing gangrene (5.75 per cent); 28 cases of threatened or impending gangrene and 89 cases of potential gangrene. Collectively, the three groups totaled 175 cases (17.3 per cent) of circulatory disturbances found. In other words, 1 out of every 17 to 18 diabetics developed gangrene and 1 out of every 6 showed evidences of impaired circulation. If the more recent 5-year-period (1926 to 1930) is considered, the incidence is higher: 6.78 per cent developed gangrene and 19.75 per cent had deficient circulation in the extremities.

The author's figures compare closely with the average statistics of others. Out of 12,037 patients with diabetes, there were 756 cases of gangrene (a percentage of 6.28).

Diabetic gangrene is the end product of three main influences: the metabolic disturbances and their effect upon the vessels and the tissues, changes in the arteries with the resulting deficient blood supply to the parts, and infection.

Of the group of patients with gangrene, all but 2 developed this complication when past 50. Gangrene may develop at any time in the aged diabetic. There were 10 cases of gangrene among those who had diabetes between 1 and 2 years, and 11 cases between 3 and 4 years.

Of the 58 cases of gangrene, 16 resulted in amputations (27 per cent).

The prognosis for the diabetic with gangrene is uncertain. There were 15 deaths in the author's series (26 per cent). This included both the surgical cases and those patients who declined operations. The future of the diabetic who has once had gangrene is fraught

with danger. He is always liable to a recurrence of the complication. The average span of life for those who have had gangrene with amputation of the extremity is considered to be about 2 years.

To lower the incidence of gangrene in the diabetic and to increase his span of life, one must have cognizance of the high incidence of circulatory disturbances in these patients. Early recognition of arterial changes and an intelligent attempt to correct and improve the circulation may ward off complications until a sufficient collateral circulation has been established to make up for the deficient blood supply to the parts.

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THE EFFECT OF LUGOL'S SOLUTION ON CHRONIC LYMPHATIC LEUKEMIA AND ITS BEARING UPON THE PATHOGENESIS OF EXOPHTHALMIC GOITER.

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The Basal Metabolism in Disease. Other than exophthalmic goiter, the basal metabolic rate is significantly elevated in various clinical conditions, such as the leukemias, polycythemia vera and the nonleukemic lymphoblastomata (Kraus,[1] Boothby and Sandiford,[2] Riddle and Sturgis,[3] Krantz and Riddle,[4] Abbott,[5] Isaacs,[6] Krantz[7]). Although there is considerable variability in the literature, the consensus of opinion is that there may be a significant increase in oxygen consumption in certain patients with pernicious anemia, essential hypertension, acromegaly and diabetes mellitus (Meyer and DuBois,[8] Boothby and Sandiford,[2] Strauss,[9] Riesman,[10] Mannaberg,[11] Boas and Shapiro,[12] Cushing and Davidoff,[13] Joslin and Lahey[14]).

The increased basal metabolic rate in exophthalmic goiter has been variously attributed either to an excess (Möbius[15]) or an abnormality (Mayo and Plummer,[16] Williamson and Pearse[17]) of thyroid secretion. Other glands of internal secretion, such as the adrenals and gonads have been considered by some as responsible for the clinical syndrome, and various portions of the central and sympathetic nervous systems have received similar attention.

There is just as little agreement, and possibly a group of more intangible hypotheses, concerning the nature and mechanism of the elevated oxygen consumption in the leukemias.

Although early investigators (Graefe[18]) suggested the relative importance of immature leukocytes in the maintenance of an increased basal metabolic rate in leukemia, subsequent clinical experience (Murphy, Means and Aub,[19] Krantz,[7] Riddle and Sturgis,[3] Krantz and Riddle,[4] McAlpin and Sanger,[20] Gunderson[21]) has demonstrated that there does not seem to be an *invariable* relationship between the total white blood cell count, state of maturity of leukocytes and the height of the basal metabolic rate. Although these factors sometimes vary simultaneously in the same direction, the association is certainly not a *constant* one.

The suggestions concerning the mechanism of the elevated basal metabolic rate in acromegaly, diabetes mellitus, essential hypertension, pernicious anemia and the nonleukemic lymphoblastomata seem to be based mostly upon speculation. However, Isaacs[6] has demonstrated in polycythemia vera that there is a definite relationship between the height of the basal metabolic rate and the uric acid production due to the destruction of nuclear material.

Finally, it seems of importance to note that the basal metabolic rate is not invariably elevated above normal even in exophthalmic goiter and the chronic leukemias; and it is also of interest that Kessel and Hyman,[22] Friedgood[23] and others have reported a clinical syndrome (autonomic imbalance, sympathotonia, formes frustes hyperthyroidism) indistinguishable from exophthalmic goiter with the exception of a normal basal metabolic rate.

It is obvious, therefore, that although considerable investigation has been directed toward the discovery of the cause or causes responsible for the increased oxygen consumption in these diverse maladies, the entire problem has successfully resisted a satisfactory solution.

Nature of the Present Investigation. The remarkable effect of Lugol's solution on the elevated basal metabolic rate, pulse rate and clinical symptoms of exophthalmic goiter naturally suggested investigation of its activity on similarly increased oxygen consumption in conditions other than Graves' syndrome. The present series of observations, therefore, were made in the belief that under properly controlled conditions, valuable information could be ascertained concerning the mechanism involved in the production and maintenance of the elevated basal metabolic rate not only in Graves' syndrome, but also in the other diseases characterized by this phenomenon. It was also hoped that further investigation would result in a clearer conception of the pathogenesis of exophthalmic goiter and the nature and significance of the iodin reaction.

Lugol's Solution in Graves' Syndrome. The effect of iodin in exophthalmic goiter is well defined and widely recognized. It is of interest, however, to emphasize several of the more significant characteristics of the iodin reaction.

Lugol's solution will depress the elevated basal metabolic rate and tachycardia, and ameliorate the peculiar nervous manifestations of the disease in favorable cases of exophthalmic goiter.

However, iodin does not always induce such a remission, nor does it materially influence the progress of the disease itself, except that it may temporarily alter the character and intensity of the symptoms (Means and Richardson,[24] Barker[25]).

Finally, there is evidence to believe that the characteristic response to iodin is dependent upon the geographic area in which the case originates (Coller and Potter[26]); and that the higher the basal metabolic rate before administration of iodin, the greater is the expected percentage drop in the rate following treatment. It is also true, conversely, that the decrease from the original basal rate is relatively small, if the initial rate was only moderately increased (Means and Richardson,[24] Coller and Potter[26]).

Effect of Iodin in Experimental Hyperthyroidism and on Normal Human and Animal Controls. These clinical observations assume even greater significance when it is emphasized that iodin has no effect whatsoever in altering the clinical symptoms, increased

basal metabolism and pulse rate induced by the ingestion of thyroid extract in man, and that it does not accelerate recovery from the true state of hyperthyroidism thus produced (Carson and Dock,[27] Sturgis,[28] Means and Richardson,[24] Starr, Walcott, Segall and Means[29]). Martin,[30] Read, Walker and McKenney,[31] Snell, Ford and Rowntree,[32] and Liebesney[33] conclude that iodin has no appreciable effect in normal human beings, and Liebesney[33] suggests that it may even be associated with a tendency to increase the basal metabolic rate.

Sturgis, Zubiran, Wells and Badger[34] and Kunde[35] have definitely demonstrated that iodin is ineffective in influencing or preventing experimental hyperthyroidism in animals, contrary to the experiments of Hildebrandt[36] and Blalock and Harrison.[37]

Lugol's Solution in Morbid Conditions Other Than Exophthalmic Goiter. Martin[30] has recorded his investigations concerning 2 cases each of "small cell" lymphatic leukemia and polycythemia vera which he treated with 5 drops of Lugol's solution 3 times a day. These patients failed to show any change in basal metabolism. However, 4 patients with pernicious anemia and 2 cases of afebrile convalescent rheumatic fever showed a definite depression in their basal metabolic rates by the 14th day of treatment.

Cushing and Davidoff[13] have reported a single case of acromegaly (hyperpituitarism) which they considered free of "hyperthyroidism," and in which the basal metabolism and pulse rate rapidly decreased following treatment with Lugol's solution just as occurs in exophthalmic goiter; however, they concluded that the elevation of the metabolic rate (+40 per cent) "might be properly ascribed to the hyperpituitarism."

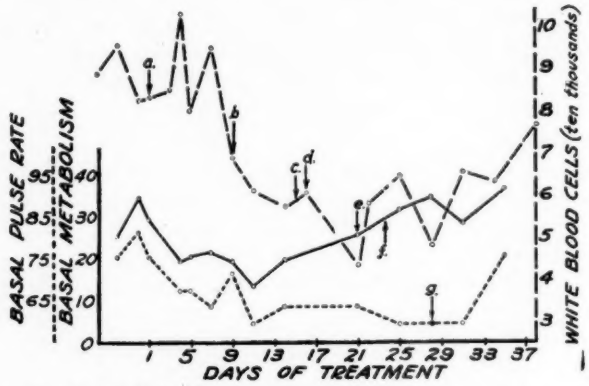
Additional experience in this clinic[38] (data unpublished as yet) shows that iodin had a definite effect in decreasing the basal metabolic and pulse rates in one case each of polycythemia vera and acromegaly. Its effect in chronic myelogenous leukemia is questionable.

Clinical Methods and Procedure. Ten patients with chronic lymphatic leukemia were treated with Lugol's solution (usually 1 cc. 2 or 3 times daily) over a period of several weeks, when the clinical condition of the patient allowed this interval of study. This procedure was not adopted in those patients suffering from severe anemia and in immediate need of transfusions.

Determinations of the basal metabolic rate, basal pulse rate, basal weight and blood studies were carried out during this period of study. The basal metabolisms were determined in the routine manner with the closed-circuit Roth-Benedict apparatus.

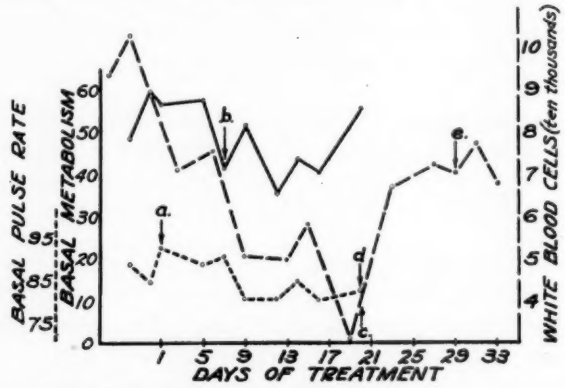
All of the patients who eventually showed a significant response to Lugol's solution were ambulatory, and in most cases attending the medical out-patient department. Nevertheless, the control period, even in these cases, extended over several days to 2 weeks.

These precautions were necessarily taken because of the widely recognized fall in basal oxygen consumption following general hospitalization and subsequent mental as well as physical relaxa-



Basal metabolism —∘— Basal pulse rate - - - ∘ - - -
White blood cells — — ∘ — —

CHART I.—*Patient No. 1.* Changes in basal metabolism, pulse rate and leukocytes during treatment. *a*, Started Lugol's solution, gtts. xv b.i.d.; *b*, Lugol's solution increased to gtts. xv t.i.d.; *c*, Lugol's solution temporarily discontinued; *d*, Vincent's angina with temperature of 102° F. Possibly an exacerbation of leukemic process; *e*, Roentgen ray treatment over inguinal lymph nodes. White blood cell count taken before treatment; *f*, Lugol's solution resumed, gtts. xv b.i.d.; *g*, persistent bradycardia associated with increased basal metabolic rate.



Basal metabolism —∘— Basal pulse rate - - - ∘ - - -
White blood cells — — ∘ — —

CHART II.—*Patient No. 2.* *a*, started Lugol's solution, gtts. xv b.i.d.; *b*, basal metabolism determined 35 minutes after 0.060 gm. codein phosphate (*h*); *c*, transfused with 500 cc. citrated blood; *d*, persistent slow pulse associated with an increasing basal metabolic rate; *e*, Lugol's solution discontinued.

tion during the test period. Any changes, therefore, that occurred in basal metabolism, pulse rate or white blood cell count could not properly be attributed to prolonged hospitalization or bed rest.

Following the control period, the basal metabolism was determined every other day, starting on the third to the fifth day of treatment, and if a depression occurred, was followed, if possible, until it had definitely ceased to exhibit changes of any significance. The white blood cell counts were studied simultaneously.

Several of the patients had received Roentgen ray therapy from 1 to several months prior to treatment with Lugol's solution, and this fact is noted in conjunction with each case report.

Clinical Data. The charts and clinical notes which follow are concerned with the case histories and physical findings of 10 patients suffering from chronic lymphatic leukemia. The salient points in their clinical course prior to and after treatment with Lugol's solution are indicated schematically in Tables 1 to 5. The complete clinical data are presented graphically in Charts I and II, and are necessarily limited to a consideration of only 2 patients in order to omit superfluous detail and repetition.

TABLE 1.—SUMMARY OF CLINICAL HISTORIES IN 10 PATIENTS WITH CHRONIC LYMPHATIC LEUKEMIA.

Clinical symptoms.	Number of patients.
Asthenia	10
Ease of fatigue	8
Unusual nervousness	8
Abnormal irritability	8
Good appetite	5
Night sweats	5
Cough with expectoration	5
Dyspnea on exertion	5
Marked loss of weight	4
Bleeding gums	4
Precordial palpitation	4
Slight loss of weight	3
Abnormal increase of perspiration	3
Subjective increase of warmth	2
Abnormal increase of appetite	2
Diarrhea	2
Epistaxis	2
No loss of weight	2
Pleurisy	2
Moderate loss of weight	1
Appearance of diffuse skin pigmentation	1
Anorexia	1

Clinical Results. *Nature of the Symptomatic Remission.* The laws which apparently govern the response of exophthalmic goiter to iodin seem to apply, with remarkable similarity, to chronic lymphatic leukemia. However, the percentage frequency of this response in leukemia is smaller than that noted in Graves' syndrome.

Investigation of this series of 10 consecutive patients with chronic lymphatic leukemia revealed the fact that each one experienced a symptomatic remission within 24 hours to 10 days after the initial treatment with iodin was instituted. In 2 of these instances, it was only of relatively brief duration (about 2 weeks).

TABLE 2.—SUMMARY OF PHYSICAL SIGNS IN THE 10 PATIENTS.

Physical signs.	Number of patients.
General glandular enlargement	10
Splenomegaly	10
Pallor of skin and mucous membranes	6
Definite malnutrition	4
Bilateral exophthalmos with relatively greater prominence of the right eye	3
Dalrymple's eye sign positive	3
Bleeding gums	3
Unilateral prominence (exophthalmos) of right eye	2
von Graefe's eye sign positive	2
Kocher's eye sign positive	2
Leukemic retinitis	2
Conjunctiva visible below cornea with axis of vision in horizontal direction	2
Enlargement of submaxillary glands	2
Bilateral exophthalmos	1
Hepatomegaly	1
Diffuse brownish skin pigmentation	1
Purpura over lower extremities	1
Chronic myocardial insufficiency with normal blood pressure	1

TABLE 3.—DATA IN THE 10 PATIENTS BEFORE TREATMENT WITH LUGOL'S SOLUTION.

Number.	Sex.	Age.	Duration of illness.	Previous Roentgen ray therapy.	Original metabolic rate (per cent).	Original pulse rate per minute.
1	Male	42	1 year	None	+29	82
2	Male	43	6 years	None	+54	88
3	Male	43	6½ years	+*	+66	88
4	Female	45	1½ years	++	+26	91
5	Male	48	8 months	None	+60	75
6	Male	62	2½ years	+	+31	78
7	Male	65	8 months	None	+41	80
8	Male	67	3 years	++++	+29	88
9	Male	57	1 year	None	+33	70
10	Male	66	6 months	None	+47	80

* + to ++++ indicates extent of previous Roentgen ray therapy.

The earliest specific activity of iodin in chronic lymphatic leukemia was found to be a beneficial effect upon the asthenia and ease of fatigue, and a definite decrease in the state of nervousness and irritability.

The signs and symptoms (profuse sweating, hot flushed skin, tachycardia, nervousness, tremor) which are generally attributed to the increased basal metabolic rate in exophthalmic goiter, are either absent or only slight in patients with leukemia and a similarly elevated basal metabolic rate (Murphy. Means and Aub[19]). Minot and Means[39] however, are inclined to believe that the similarity in symptoms manifested by both diseases is much more striking. Our own experience, with the present series of patients (*vide supra*), leads us to suspect that the signs and symptoms of chronic lymphatic leukemia are strikingly similar in *quality* to those noted

in exophthalmic goiter, and differ only in a *quantitative* manner, usually being much less intense even in the presence of an equally elevated basal metabolic rate.

TABLE 4.—HEMATOLOGIC DATA IN THE 10 PATIENTS.

Number.	Hemoglobin in per cent (Sahli).	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Per cent lymphocytes.	Per cent polymorphonuclear neutrophils.	Type of lymphocytes.
1	89	4.90	88.9	93	5	Large young cells. No lymphoblasts.
2	40	2.01	102.4	89	9	Young cells with very large nucleus. No lymphoblasts.
3	30	2.00	13.5	59	34*	Primitive cells with blue cytoplasm; but no true lymphoblasts.
4	70	4.58	86.4	96	2	Large young cells. No lymphoblasts.
5	35	2.18	44.8	89	8	Atypical lymphocytes. Nucleus irregular in outline and quite large, almost filling cell.
6	83	4.27	118.0	90	6	Primitive cells with large nuclei and bluish cytoplasm. No lymphoblasts.
7	64	4.16	36.0	83	16	Fragile lymphocytes, some with large nuclei and bluish cytoplasm; others with much cytoplasm and small nuclei.
8	68	3.79	200.0	98	2	Mature lymphocytes with moderate number atypical forms.
9	60	4.12	114.6	99	1	Large young lymphocytes. No lymphoblasts.
10	40	2.48	166.4	98	2	Primitive cells, dark blue cytoplasm.

* Temporary effect following early Roentgen ray treatments.

This observation suggests that these signs and symptoms are not entirely dependent upon the height of the basal metabolic rate in either disease. It seems more probable that the basal metabolic rate and clinical phenomena are dependent in great measure upon a fundamental disturbance which is common to both of them, but which may vary its expression independently under given conditions.

The Iodin Effect in a Goitrous Area. Six of the 10 patients showed a definite and significant decrease in basal metabolic rate, but in only 4 of these did the pulse rate follow this depression (*vide infra*).

The basal metabolic rate in chronic lymphatic leukemia usually begins to fall between the 4th and the 9th day, and reaches its lowest level between the 7th and the 16th day. In 1 patient the initial decrease was delayed until the 14th day.

It is of considerable interest to note that the fall in basal metabolic rate, as well as the period over which this occurs, is directly comparable to similar statistics reported by Means and Richardson,[24] and Coller and Potter[26] (Table 6) for patients with exophthalmic goiter under treatment with Lugol's solution. It seems of import-

ance, too, to point out that the present series of patients with chronic lymphatic leukemia responded to iodin more nearly like patients with exophthalmic goiter originating in a goitrous region (Coller and Potter[26]) than like those reported by Means and Richardson[24] for a nongoitrous area. The patients with leukemia were all residents of the state of Michigan and were treated under conditions similar to those cases of exophthalmic goiter which were studied by Coller and Potter.[26] It is probable that minor discrepancies in the manner of response of these patients to iodin would disappear if the number of cases of leukemia (10) was more comparable to those of exophthalmic goiter (128).

TABLE 5.—THE CLINICAL CHANGES FOLLOWING TREATMENT WITH LUGOL'S SOLUTION.

Number.	Days of treatment.	White blood cells in thousands per cubic millimeter.	Basal metabolic rate in per cent.	Basal pulse rate per minute.
1	0	88.9	+29	82
	11	61.6	+13	64
	31	43.0	+25	68
	35	62.8	+36	80
2	0	102.4	+54	88
	12	49.2	+35	80
	19	30.3	+55	82
	26	72.0	....	....
3	0	13.5	+66	88
	5	.....	+68	95
	10	16.8	+34	108
4	0	86.4	+26	91
	14	83.0	+19	88
	23	115.0	+31	88
	29	190.0	....	....
5	0	44.8	+60	75
	4	60.6	+20	77
	11	62.8	+35	78
6	0	118.0	+31	72
	15	.....	+10	62
	22	112.0	+ 4	68
	52	130.0	+52	76
7	0	36.0	+41	80
	9	.....	+49	200*
	14	.....	+43	86
* (Patient developed attacks of paroxysmal tachycardia during basal metabolism.)				
8	0	200.0	+29	88
	14	181.0	+33	86
	16	118.0	....	..
	17	94.2	+41	88
9	0	114.6	+33	70
	8	70.3	....	..
	11	47.8	+39	68
	13	55.3	+35	72
10	0	166.4	+47	80
	8	211.5	+48	89

The following tabulation (Table 6) records the original basal metabolic rates in groups of 10 per cent, and the points to which they decreased following treatment with Lugol's solution. The number of days which elapsed between the former and the latter are also recorded in each instance.

TABLE 6.—THE CHANGES IN METABOLIC RATE DURING TREATMENT.

Original basal metabolic rates in groups of 10 per cent.	Final basal metabolic rates in per cent following iodin in exophthalmic goiter.				Final basal metabolic rates in per cent following iodin in chronic lymphatic leukemia.		
	Means and Richardson (128 cases).	Days.	Coller and Potter (128 cases).	Days.	Present series.	Days.	No. cases.
80 to 90 per cent	+34	10	+38	17	....	..	0
70 to 80 "	+24	10	+48	12	....	..	0
60 to 70 "	+26	10	+40	14	+26	7	2
50 to 60 "	+24	10	+39	14	+35	12	1
40 to 50 "	+18	9	+30	12	....	..	0
30 to 40 "	+15	8	+23	16	+10	16	1
20 to 30 "	+17	8	+17	10	+16	12.5	2

It is quite possible that the widespread and constant use of iodized salt may be one of the factors responsible for the delayed and diminished effect of Lugol's solution in cases from the goitrous areas.

The Basal Pulse Rate. Iodin was effective in reducing the pulse rates of 4 patients, and ineffective in 2 others. It might conceivably have been responsible for a more rapid pulse rate in 4 other patients, one of whom developed repeated attacks of paroxysmal tachycardia. The occurrence of a striking bradycardia, which persisted in the face of an increasing basal metabolic rate, following treatment with Lugol's solution, seemed to be a significant phenomenon.

It has been generally accepted that the elevated basal metabolic rate is directly responsible for the tachycardia with which it is so closely associated, especially in cases of exophthalmic goiter and possibly in the leukemias (Sturgis and Tompkins,[40] Minot and Means[39]). Although there is no doubt concerning the relationship which Sturgis and Tompkins have pointed out, those cases which do not follow the general rule suggest that an additional factor may play an important rôle in the tachycardia of exophthalmic goiter, and more especially of chronic lymphatic leukemia.

As a general rule, the pulse rate is well above 90 or 100 per minute in frank cases of exophthalmic goiter with a significantly elevated basal metabolic rate. Only 1 of the 10 patients with chronic lymphatic leukemia showed a basal pulse rate of slightly over 100 per minute, in spite of the fact that 5 of the original basal metabolic rates were recorded between 40 and 65 per cent, 3 rates over 30 per cent, and 2 others about 25 per cent. The combination of a severe anemia, moderate elevation of body temperature and the

possibility of an iodin reaction suggested themselves as possible explanations for this single case of tachycardia.

These observations seem definitely indicative of the fact that the pulse rate is not entirely dependent upon the height of the basal metabolic rate. It is probable, that a disturbance similar to that which causes the elevated basal metabolic rate is also responsible for the tachycardia with which it is often, though not necessarily, associated; and that iodin, while tending to decrease both of them, may have a variable influence.

The Blood Picture. In 4 cases there was an unmistakable decrease in the total white blood cell count, beginning between the 3rd and 9th day, reaching its lowest level about the 20th day, and thereafter gradually increasing to approach its original level after 4 or 5 weeks. In three instances, there seemed to be an actual exacerbation in the numbers of the leukocytes following treatment with Lugol's solution. This took place in spite of the symptomatic remission which was present at the time.

Apparently the decrease, when it does take place, is at the expense of the lymphocytes. Occasionally we have noted the appearance of small numbers of eosinophils and basophils in the peripheral blood stream, following treatment with iodin, but this is not a constant finding.

A marked secondary anemia was present in 7 of the 10 cases which were studied. In three instances, originally without anemia, the red blood cell count and per cent hemoglobin appeared to decrease temporarily following iodin therapy.

It seems of interest to note that iodin therapy appeared to exaggerate the hemorrhagic diathesis which was already present in 1 or 2 of the patients with chronic lymphatic leukemia. Although this association may have been coincidental, it is significant to note that the literature repeatedly mentions potassium iodid as an etiologic factor in hemorrhagic purpura (Ricord,[41] Stengel[42] (complete bibliography)). Jackson[43] has recently called attention to a similar accident in the treatment of exophthalmic goiter with Lugol's solution.

The effect of iodin in reducing the red blood cell count and hemoglobin percentage, and in inducing hemorrhagic manifestations, suggests that this drug may play an important rôle in hemopoietic metabolism.

Regional Lymph Nodes. In 2 cases there was a partial but unmistakable diminution in the size of the cervical lymph nodes bilaterally. The other lymph glands of the body did not show any appreciable changes. Within 2 weeks there was a rapid increase in the size of these cervical glands either in spite of, or because of, the iodin therapy. The significance of this change is uncertain because variations of this type may occur spontaneously (Minot and Isaacs[44]).

Splenomegaly. There were no systematic observations carried out upon the size of the spleen in chronic lymphatic leukemia following treatment with iodin. However, the author has since noted a remarkable decrease in the size of 2 splenomegalies of unknown origin, and a third instance in a patient with chronic myelogenous leukemia, following the administration of Lugol's solution over a period of 1 to 3 weeks. Further observations are now being carried out along this new line of investigation, concerning splenomegalies not due to syphilis or tuberculosis.

The Sympathetic Nervous System. Vasomotor Phenomena. In 2 cases, the patients noted a distinct difference in the skin color, moisture and temperature of their hands before and after treatment with iodin. Originally, both of these patients had complained of pale, cold, rather dry hands, indicative of vasoconstrictor hyperactivity with spasm of the peripheral bloodvessels. Within a few days after treatment was instituted, the palms of the hands changed noticeably, with the appearance of diffuse erythema, slight moisture and increased warmth; and similar changes (not as striking) appeared over the face and ears.

Emotional Instability. A surprising number of patients (8) complained of nervousness and irritability which they had noticed since the onset of their illness. In every case, a marked remission brought definite relief from the emotional instability which they had experienced. In two instances it was only temporary, and was followed within a few days by a definite exacerbation, which later responded favorably to Roentgen ray therapy and transfusion.

Ocular Phenomena. A large number of patients had one or more of the eye signs indicative of a hyperactive sympathetic nervous system,[23] such as, bilateral exophthalmos, unilateral exophthalmos (usually the right eye), lid lag, lidspasm,[23] Kocher and Dalrymple eye signs. It is of interest that unilateral prominence of the eyes and lid lag occasionally decreased following iodin therapy. However, judging from the well-recognized inconstancy of these ocular phenomena,[23] it is uncertain whether or not this was a spontaneous change.

Response to Iodin Controlled by Unknown Factor. Earlier studies upon the effect of Lugol's solution in chronic lymphatic leukemia suggested that severe anemia, previous Roentgen ray therapy and acute exacerbations of the disease acted in an inhibitory manner upon a complete remission. Subsequent investigation, however, has not produced a constant method for predicting the type of response, if any, which one may expect in individual instances.

Conclusions and Summary. The present paper has been designed primarily for the purpose of directing attention to another point of view from which one may regard the clinical phenomena and pathogenesis of exophthalmic goiter and chronic lymphatic leukemia, with special reference to: (*a*) The mechanism of the elevated basal

metabolic rate in disease; (*b*) the significance and mechanism of the iodin effect in Graves' syndrome and chronic lymphatic leukemia, and (*c*) the relation of the sympathetic nervous system to the obvious clinical phenomena of exophthalmic goiter and chronic lymphatic leukemia.

1. The basal metabolic rate may be elevated in many clinical conditions other than exophthalmic goiter (chronic lymphatic and myeloid leukemia, nonleukemic lymphoblastomata, polycythemia vera, pernicious anemia, essential hypertension, acromegaly, diabetes mellitus and convalescent afebrile rheumatic fever). Conversely, all of these maladies, including exophthalmic goiter, may occur without an elevated oxygen consumption.

2. Lugol's solution (iodin) has a definite beneficial effect upon the clinical signs and symptoms of exophthalmic goiter. It also depresses the elevated basal metabolic and pulse rates in pernicious anemia, acromegaly and polycythemia vera. However, iodin has no effect whatsoever upon the basal metabolism and pulse rates of normal individuals, nor does it decrease the elevated basal metabolism and tachycardia of experimental hyperthyroidism induced by active thyroid substance.

3. Ten patients with chronic lymphatic leukemia were systematically studied during treatment with Lugol's iodin solution. Clinical notes were recorded concerning individual variations in clinical symptoms, physical signs and laboratory data. The basal metabolic and pulse rates were studied carefully with special emphasis upon the control period.

4. The basal metabolic rate was found definitely elevated in every patient with chronic lymphatic leukemia, but the initial basal pulse rates were not significantly increased.

5. The physical signs and clinical symptoms of chronic lymphatic leukemia are strikingly similar in *quality* to those noted in exophthalmic goiter, and differ only in a *quantitative* manner. They are usually much less intense in chronic lymphatic leukemia *even in the presence of an equally elevated basal metabolic rate.* These observations indicate that the basal metabolic rate and the other clinical manifestations of these maladies (emotional instability, tachycardia, exophthalmos and associated eye signs, profuse sweating, and vasoconstrictor phenomena) are dependent in great measure upon a fundamental disturbance which is common to all of them; and that the elevated basal metabolic is not responsible for the clinical phenomena of these maladies.

This fundamental disturbance appears to be expressed through a hyperactive state in the sympathetic nervous system, and the resultant phenomena seem to vary independently of each other under conditions which are unknown at the present time.

6. The laws which apparently govern the response of exophthalmic goiter to iodin seem to apply with remarkable similarity to

chronic lymphatic leukemia. However, the percentage frequency of this response in leukemia is smaller than that noted in Graves' syndrome.

7. In a certain percentage of the patients with chronic lymphatic leukemia, iodin will induce a symptomatic remission and a temporary decrease in the basal metabolic and pulse rates, in addition to a transient reduction in the size of the cervical lymph nodes and in the height of the total leukocyte count. It also appears that night sweats may vanish, and certain types of splenomegaly decrease under the influence of iodin therapy.

8. Iodin therapy may, however, exaggerate the hemorrhagic diathesis already present in chronic lymphatic leukemia, and in certain instances induce a decrease in the red blood cell count and hemoglobin. This drug may also cause an exacerbation of those factors (emotional stability, pulse rate, basal metabolic rate and white blood cell count) upon which it sometimes acts in a sedative manner. The mechanism of this paradoxical activity remains unknown.

9. The thyroid gland is not only remarkable for its avidity in storing iodin (Marine and Lenhart[45]), but also for the fact that the epithelial changes in its structural conformation (colloid resting type or hyperplastic and hypertrophic states) may be directly dependent upon the presence or absence of available iodin both in cases of simple endemic and exophthalmic goiter (Marine,[46] Rienhoff,[47] Cattell,[48] Kocher[49]).

One must not confuse this issue by assuming that the activity of the iodin is limited to functions of the thyroid gland, just because the latter is capable of *storing* iodin with unusual facility. Their relationship is probably similar in some respects to that which is known to exist between glycogen and the liver.

Results of the present investigation indicate that the specific beneficial effects of iodin in exophthalmic goiter, chronic lymphatic leukemia, polycythemia vera, acromegaly and pernicious anemia are probably not exerted through the influence of the thyroid gland.

10. One of the most striking effects of iodin in exophthalmic goiter and chronic lymphatic leukemia is its "sedative action" upon the signs and symptoms of sympathetic nervous system hyperactivity (tachycardia, tremor, abnormal sweating, emotional instability, vasomotor phenomena, exophthalmos and associated eye signs). The specific activity of iodin is probably closely related to the physiology of the sympathetic nervous system.

11. The available evidence suggests that exophthalmic goiter is not caused by disease of the thyroid gland. The sympathetic nervous system apparently plays a major rôle in the pathogenesis of Graves' syndrome, and is probably also a factor of importance in chronic lymphatic leukemia.

In evaluating these conclusions, it must be remembered that the

level of the basal metabolic rate is subject to capricious changes. Consequently, the results of the present investigation are of a tentative character from this point of view, and await further and extensive experimentation for confirmation. Nevertheless, there can be little real doubt concerning the beneficial effect of iodin upon the clinical symptoms, and its tendency to decrease the pulse rate and white blood cell count in certain instances of chronic lymphatic leukemia. In any event, the striking clinical parallelism which exists between exophthalmic goiter and chronic lymphatic leukemia is deserving of more critical scrutiny.

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FOOD ALLERGY IN THE DIFFERENTIAL DIAGNOSIS OF ABDOMINAL SYMPTOMS.*

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Food allergy is not infrequently the cause of acute abdominal pain and vomiting and of many other persistent gastrointestinal symptoms.[1] It is indeed probable that such symptoms are the most frequent evidences of food allergy because of the intimate contact that allergy producing foods have with the gastrointestinal membranes. Surgeons as well as internists, therefore, must ever keep food allergy in mind in the differential diagnosis of all abdominal symptoms.

Literature. My attention was first directed to gastrointestinal food allergy by Schloss in 1915[2] and Cooke[3] in 1917. In 1921 to 1923, Duke[4,5,6] stressed this cause of acute abdominal pain and other symptoms in three contributions. His article on abdominal pain was of special value. In 1925 a study of 234 patients with bronchial asthma allergic indigestion was noted by me[7] in 12 per cent. In 1927 and 1928 I discussed the rôle of food allergy in the production of abdominal symptoms in 5 articles,[8,9,10,11,12] in 1 of which[10] 50 cases with such symptoms were reported. Recently, in my book on "Food Allergy,"[1] statistics on 100 patients with gastrointestinal allergy were presented, and an extended discussion of the entire subject with 21 case reports was included. Andresen in 1925[13] wrote a comprehensive article on gastrointestinal allergy. Eyermann,[14] in 1927, discussed the various gastrointestinal symptoms in allergic patients. Vaughan[15] reported mucous colitis due to food allergy in 1928. In 1930[16] he discussed the rôle of food allergy

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in abdominal as well as general symptoms. Balyeat,[17] in 1930, also emphasized gastrointestinal food allergy. Charles Richet, who coined the word anaphylaxis in 1902, was one of the first to describe gastrointestinal symptoms due to food allergy and his views were presented by Barnathan[18] in a thesis on the subject in 1911 and again by Laroche, Richet and Saint Girons[19] in 1919. These contributions, as well as those of Schloss,[20] described the various gastrointestinal symptoms of food allergy in childhood. Recently, in 1931, Stafford, Jacobus and Watson[21] again discussed these manifestations in childhood.

Clinical Observations. In my recent discussion of gastrointestinal food allergy[22] an analysis of 50 of the records of a series of 100 patients with such disorders revealed the occurrence of the following symptoms:

Canker sores, 20 per cent; coated tongue, 18 per cent; heavy breath, 14 per cent; distention, 32 per cent; belching, 20 per cent; sour stomach, 18 per cent; epigastric heaviness, 28 per cent; burning or pyrosis, 14 per cent; nausea, 40 per cent; vomiting, 30 per cent; intestinal cramping, 24 per cent; mucous colitis, 14 per cent; diarrhea, 12 per cent; constipation, 32 per cent; proctitis, 2 per cent; pruritus ani, 4 per cent; pain and soreness in the epigastrium, 20 per cent; in the upper right quadrant, 14 per cent; in the mid-abdomen, 10 per cent; in the lower abdomen, 20 per cent, and an ulcer type of pain, 10 per cent. Symptoms including weakness, fatigue, irritability, nervousness, mental dullness and confusion and generalized aching due to "allergic toxemia" from food were present in a number of these patients. All of the above symptoms have been found in another series of 150 patients, statistics of which have recently been published.[1] My findings are quite like those reported by Eyermann[14] in 1927. A family history of allergy was present in 65 per cent of the patients and a personal history of asthma, hay fever, cutaneous allergy or migraine was present in from 13 per cent to 36 per cent. My studies[23] indicate that allergic patients often inherit the tendency to develop a specific type of allergy such as food or pollen allergy as well as a specific localization of its manifestations such as hay fever or migraine. Thus it is interesting that patients with gastrointestinal allergy often give a history of chronic abdominal disturbances in their forebears which resemble those of the patient.

It is also interesting that Lintz states in 1925[24] that a family history of chronic appendicitis should suggest allergy rather than infection as the underlying cause. It must be emphasized, however, that certain patients with gastrointestinal and other manifestations of allergy have no personal or family history of allergy.

Gastrointestinal Food Allergy from the Surgeon's Viewpoint. Special comment on the various manifestations of gastrointestinal food allergy is important in order to indicate the necessity of the constant

consideration of this etiologic factor in differential diagnosis. Acute as well as mild and chronic manifestations will be discussed in this paper. It is well to remember that allergy produces two main reactions in tissues which give rise to its symptoms—first, edema of mucous membranes and other tissues with the concomitant production of mucus and disturbed membrane permeability, and second, smooth muscle spasm which may occur in any tissue containing such smooth muscle from the bronchi or arteries to the gastrointestinal or urogenital tracts. The mucous membranes and the abundant smooth muscle of the digestive tract, therefore, are natural sites for the establishment of allergic reactions from foods. It is probable that lesions similar to urticaria, erythema and even eczema in the skin may occur in the various parts of the gastrointestinal tract. Angioneurotic edema has been observed at operation for supposed obstruction.[25]

It is likely that allergic reactions to bacteria and other allergens than food may produce symptoms in various parts of the gastrointestinal tract. Pollen allergy has produced symptoms in a few of my patients as well as patients of other observers.[26] However, food is the outstanding cause of allergic digestive symptoms and our discussion will be confined to such etiology.

1. Gastric Symptoms. I have reported food allergy as a frequent cause of distention, belching, pyrosis, epigastric heaviness, nausea, vomiting and sour stomach. Such symptoms may be mild or severe and may occur immediately or be delayed for 1 to 3 hours. The digestive disturbances and especially definite food intolerances in infancy are frequently due to food allergy and it is probable that many cases of pylorospasm are due to allergic edema and smooth muscle contraction. The frequency of canker sores, white coatings on the membranes of the mouth and gums, and coated tongues in patients with abdominal allergy deserves mention at this place. The possible relation of canker sores to peptic ulcer will be discussed later. The gastrointestinal symptoms so frequently associated with migraine have been relieved through my "elimination diets." It is my opinion[27] as well as that of Balyeat[28] that most cases of migraine are due to food allergy.

2. Intestinal Symptoms, Vomiting and Anorexia. It is probable that nausea due to food allergy may arise in certain patients from disturbed peristalsis in the small intestine or in the stomach. Colic, cramping, abdominal pain and mucous colitis may be due to similar reactions. My Roentgen ray studies of certain patients[29] with gastrointestinal allergy have revealed moderate duodenal stasis and reversal of peristalsis as well as hyperperistalsis and hypermotility, which apparently depended on the inclusion of allergy-producing foods in their diets. Further Roentgen ray studies on the small intestine in patients with gastrointestinal allergy are in progress.

3. Colonic Symptoms. The spasm and mucus of mucous colitis can well be explained by food allergy. Such etiology has been reported by Duke[4] in 1921, Vaughan[30] in 1922 and 1928, Richet[31] in 1926, Hollander[32] in 1927, the writer in 1928, Beecher[33] in 1928 and Balyeat[17] in 1930. Pain, soreness and disturbed peristalsis are at times due to this condition which may not be readily recognized. I have discussed mucous colitis[34] in my recent monograph, and case reports have been included. It is probable that the so-called irritable bowel for which no satisfactory etiology has ever been presented often may be due to food allergy.[35] Many of my patients affected with food allergy have suffered with colonic pain and tenderness and other symptoms characteristic of the irritable bowel. Right-sided abdominal pain[36] and soreness due to allergic reactions in the ascending colon occur frequently and will be referred to later. Disturbances in the harmonic peristalsis in the colon due to food sensitizations as observed in the Roentgen ray have been described by Eyermann.[14] Pruritus ani due to food allergy was described by Andresen in 1925.[13] In 1928[10] I reported such etiology and Vaughan[16] in 1930 reported several cases. Pruritus ani due to allergy is an example of the usual tendency to the localization of allergic reactions. Idiopathic bleeding from the intestinal tract has been described by Lintz.[37] Other idiopathic hemorrhages in allergic patients have been discussed in my recent book.[38] Finally, food allergy has been a frequent cause of constipation in my patients due to spasm in the colonic musculature.

4. Abdominal Pain and Soreness. The cause of abdominal pain and soreness is a constant challenge to every surgeon and physician. Food allergy is a frequent cause of these symptoms and must always be considered in the differential diagnosis.

(*a*) Abdominal pain suggesting appendiceal inflammation may be due to food allergy. It is not surprising that the ascending colon and especially the cecum are frequently the seats of reactions due to food allergy since the food residues remain in contact with these tissues for many hours in normal patients.

Allergic reactions in the cecum probably extend into the appendix as well and it is entirely probable that the resulting edema and spasm may predispose to infection. As already stated, Lintz[24] feels that many appendectomies are done because of allergic reactions in the colon and appendix. My experience also shows that pain and soreness in this region may be due to allergy alone. Acute allergic[39] reactions moreover may be accompanied by fever, a leukocytosis of 12 to 20,000, though the polymorphonuclears are usually below 80 per cent. Many so-called cases of chronic appendicitis are also probably due to food allergy. Allergic reactions in the appendix and cecum may predispose to bacterial invasion, especially when resistance to such infections is naturally low or diminished. When definite rigidity is present, however, and other indications of an

acute appendicitis are found surgery should never be postponed even when allergy is suspected.

(*b*) Abdominal pain and soreness suggesting gall bladder disease may also be due to food allergy. Allergic pain in the upper right quadrant is usually dull, though it is at times severe. There is frequently a rather constant pain and soreness in this area and over the whole region of the liver, such as I reported in 12 patients in 1928[10] due to food allergy. Severe pain suggestive of gall-stone colic has not been observed in my work. The whole right side of the abdomen may be affected. Graham, Cole, Copher and Moore[40] have reported similar observations of Alexander and Eyermann. They list intestinal allergy as a third consideration in their differential diagnosis of cholecystitis. As I have recently stated, it is probable that allergic reactions occur in the liver itself. Patients with chronic food allergy, especially those with severe "bilious headaches," are at times moderately jaundiced, indicating swelling of the parenchyma of the liver with edema or spasm of its ducts. Other evidence in favor of hepatic allergy has been reviewed elsewhere.[41] Pain and soreness in the upper right quadrant may also be due to colonic reactions as reported by Eyermann and observed in my own studies and it must be mentioned that Duke[42] and I have reported renal colic due to food allergy.[43] Thus pain and soreness in the upper right quadrant, especially in a patient with active or potential allergy should suggest food allergy as a possible cause.

(*c*) Abdominal pain suggesting peptic ulcer may be due to food allergy. Such pain occurred in 5 patients as recently reported in my series of 50.[44] In 1 of these patients, in whom a provisional diagnosis of ulcer was made some years before, an unnecessary exploratory operation was performed because of sudden severe pain, which was attributed to possible perforation. Since then his pain has been shown to be due to wheat allergy.

The association of food allergy and peptic ulcer has come to my attention several times. Carr,[45] in 1926, reported milk allergy in a patient with ulcer, in whom severe headache, nausea, drowsiness, urticaria, tender painful joints and a temperature of 101.2° F. developed whenever he was placed on a milk régime. Sterling, in 1929,[46] reported 2 such cases and I have recently recorded 2 others.[47] Kern and Stewart[62] have recently reported on the incidence and significance of food hypersensitiveness as observed in 32 patients with duodenal ulcer.

I have stated in 1928[10] and again in 1931[48] that canker sores are frequently due to food allergy. Andresen, in 1925,[13] affirmed such etiology. I have also suggested that lesions similar to canker sores could readily occur in the stomach or duodenum and that the continued action of the digestive ferments on such sores could produce peptic ulcers of varying degrees. This possibility is receiving further study.

(*d*) Abdominal pain and soreness due to food allergy may occur in other parts of the abdomen than those already discussed. Such symptoms in the upper left abdomen have been observed in 4 patients,[49] probably due to colonic reactions. Mid-abdominal and left-sided pain may also occur. Three patients with recurrent severe attacks of pain localized in a small area to the left and just below the umbilicus in whom food allergy was the sole cause have been reported.[49]

Pain in the lower abdomen may be due to food allergy localized in the descending colon or sigmoid or small bowel. Rectal spasm and tenesmus with pain referred to the back is not infrequently due to food allergy. Lower abdominal pain and soreness may be due to bladder[50] or uterine allergy,[51] producing painful burning urination and painful disordered menstruation.

Angioneurotic edema may cause severe abdominal pain and signs of intestinal obstruction as I have previously reported. Such lesions have been discovered at exploratory operations. Osler,[52] in several articles, warned against surgery in patients with visceral manifestations of the erythema group of skin diseases, and in 1914[53] he predicted that anaphylaxis would probably explain such symptoms. Food allergy has been shown by Alexander and Eyermann[54] to be a definite cause of Henoch's purpura and angioneurotic edema is frequently due to food allergy in my experience and that of other students of the subject. As a cause of acute or severe abdominal pain, therefore, food allergy must be kept in mind by all surgeons in order to prevent unnecessary operative procedures. This is especially true when physical findings do not correspond with the degree of severity of the presenting symptoms. Many exploratory operations with negative findings have been done because of allergic symptoms.

Diagnosis. Before outlining the various criteria which should direct the physician's attention to the possibility of food allergy in his patient, it must be emphasized that complete and painstaking physical and laboratory examinations must be done to determine all types of existing lesions. This is most important before food allergy as a cause of the various symptoms which have been discussed in this paper can be definitely considered. Such studies should include a careful history and physical examination, a stomach analysis, stool analyses, Roentgen ray studies of the gastrointestinal tract of the colon by means of a barium enema and gall bladder studies preferably with the intravenous dye. Proctoscopic examinations and other laboratory studies should be done when indicated. I have recently discussed the importance in Roentgen ray studies of a menstruum for barium to which the patient is not allergic. The use of milk in patients sensitive to it produces peristaltic disturbances which may confuse the roentgenologist.

The presence of definite lesions in the gastrointestinal and biliary tracts does not rule out the presence of food allergy. This was stressed by Duke[42] and I can corroborate his opinion. As already stated, allergic reactions may predispose to appendicitis, cholecystitis and initiate peptic ulcer. Thus it is necessary at times to carry out surgical or medical therapy for definite pathologic conditions as well as modify the diet to control food sensitizations.

What should make the physician suspect allergy in his patient?

1. A personal or family history of asthma, hay fever, urticaria, eczema, migraine or of recurrent colds or coughs and in certain instances of chronic gastrointestinal symptoms should suggest potential allergy in the patient. I have repeatedly stated that the general history of every patient studied by physicians should offer evidence that careful questioning for such potential or active allergy has been made. Possible allergy of all types including food allergy is extremely common, as shown by my recent analysis[56] of 400 college students in whom potential allergy was present in 58 per cent.

2. The history of definite food disagreements and dislikes should suggest the possibility of allergy. Here the rôle of inadequate digestion and nervousness must be kept in mind, but allergy is more often indicated by such history than is appreciated.

3. Skin testing with foods should be done. I have stressed for several years the frequency of negative cutaneous, and to a definite though less extent, of negative intradermal reactions to food allergens to which sensitization exists. The necessity of diet trial has been emphasized by me as well as by Brown,[57] Alexander[58] and Eyermann[59] where negative as well as positive skin reactions occur. These negative reactions depend on the localization of the allergic disturbances in the special tissues rather than in the skin, as pointed out by Alexander[60] in 1928. My continued experience indicates that skin reactions should be carried out when possible, though they are rarely of much help in the study of patients with gastrointestinal allergy.

The determination of food allergy, therefore, must be made with diet trial. For this my "elimination diets" have been of increasing service. Many obscure symptoms have been found due to food allergy by means of these diagnostic diets. Treatment of food allergy requires a gradual development of such "elimination diets" with the gradual determination of the specific foods which are productive of the symptoms. Desensitization to such foods may result from their prolonged elimination from the diet or may be accomplished by gradual feeding.

Summary. 1. Many gastrointestinal symptoms have been discussed which may be due to food allergy.

2. The realization that food allergy can produce a wide variety

of gastrointestinal symptoms necessitates the consideration of this etiology in the differential diagnosis of abdominal complaints.

3. These symptoms frequently simulate acute or chronic abdominal lesions and have led to many unnecessary operations in the past.

4. The necessity for the study of every patient with potential or active allergy in mind is paramount. Positive or negative evidence of such allergy should be included in the family and personal history of every patient.

5. Because of the frequency of negative skin reactions in food allergy the use of "elimination diets" for diagnosis has been found of increasing value.

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SYPHILITIC ARTHRITIS WITH EFFUSION.

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The literature can be summarized in the following sentence: Syphilitic arthritis can imitate every form of joint disease. Finger,[1] Frauenthal,[2] Hartung,[3] Schlesinger,[4] Todd[5] and others recognize acute febrile affections, resembling infectious arthritis; subacute forms simulating rheumatoid (atrophic) arthritis; chronic types with the clinical appearance of (hypertrophic) osteoarthritis. The affection can be monoarticular, symmetrical or polyarticular. The intensity of involvement varies from simple effusion to gummatous granulation and finally to destructive processes of the membrane and articular surface with deformity and ankylosis. The diagnosis is based on peculiar clinical features, response to treatment, Roentgen ray findings and the Wassermann reaction in blood serum and joint fluid.

The evidence, however, is at best sufficient to identify only a fraction of the types enumerated above. The pathologic foundation is inadequate, consisting of a limited number of older descriptions of gross specimens demonstrating gummatous involvement or chondritis (Lancreau,[6] Virchow,[7] Gangolphe,[8] Gies,[9] Chiari,[10] Kaufmann,[11] Schmidt[12]). Only a few microscopic studies were reported.

The estimation of frequency also is subject to extreme variations. Stein[13] calculated syphilitic arthritis to amount to 20 per cent of all forms; Brunauer and Hass,[14] to 2 per cent of their material. The elusive and complex clinical description, the discrepancies and difficulties of detection have had the result that the whole subject was almost lost sight of. The impression is prevalent, that tabetic arthropathy is the only manifestation of syphilitic joint disease. This is liable to cause grave consequences, as syphilitic arthritis often yields to proper treatment only, if recognized in an early stage. Reinvestigations are indicated to clarify and to amplify our knowledge of syphilitic arthritis. It is thought that this can be accomplished by the analysis of well-defined forms on the basis of a broad material. My study is devoted to a consideration of the type of syphilitic arthritis with effusion as the main clinical feature. This permits one to base the diagnosis by correlation of clinical findings with the findings in the joint fluids and to consider this type of syphilitic arthritis as a sector of the whole group of arthritides with effusion.

Analysis of the Material. The material for this investigation consists of 112 cases of acute and chronic arthritis with effusions of various etiology. The details will be found in Table 1. Nine

cases were diagnosed as syphilitic arthritis; seven cases of simple synovitis; the 8th is combined with a juxta-articular gumma; the 9th is a case of synovitis with osteochondritis and periostitis. In addition we shall discuss a case of synovitis with gumma at the articular surface of the femur and 2 cases of tabetic arthropathy not included in this series.

TABLE 1.—DIFFERENTIAL DIAGNOSIS OF 112 CASES OF ARTHRITIS WITH EFFUSION.

	Acute and subacute.		Chronic.		All forms.	
Etiology.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
"Nonspecific"	35	31.0	49	44.0	84	75.0
Doubtful	1	0.9	5	4.4	6	5.3
Tuberculous	1	0.9	4	3.6	5	4.4
Gonorrheal	6	5.4	1	0.9	7	6.3
Tabetic	0	..	1	0.9	1	0.9
Luetic	4	3.6	5	4.4	9	8.1
Total	47	41.8	65	58.2	112	100.0*

* Percentages carried out to tenths only.

A. SYPHILITIC SYNOVITIS.

Case Reports. CASE 1.—V. K., girl aged 6 years. Her mother had miscarriages before and after the child's birth and her blood Wassermann was strongly positive. Three months before admission to the Clinic the child developed a bilateral eye condition, which was diagnosed as parenchymatous keratitis. Wassermann and Kahn tests were 4+ in the blood. She received 6 injections of arsphenamin. During treatment and 2 weeks before entering the Clinic, she developed swelling of both knees, almost painless. Each knee was distended, especially over the suprapatellar bursa. There was no marked increase of temperature or thickening of the synovial capsule. Twenty cubic centimeters of a slightly cloudy, greenish fluid were aspirated from the left knee joint. It contained a dense fibrinous net. The Wassermann was 4+ in the joint fluid and in the blood. Roentgen ray was negative. For other findings see Table 2. The patient continued the antiluetic treatment with the addition of mercury inunctions. One month later the swelling disappeared and the Wassermann in the blood returned to negative. Check-up examination in 3 months showed a normal condition of the joints.

CASE 2.—C. I., boy aged 8 years. His mother stated that 6 weeks previously the child fell and subsequently developed pain and swelling of the left knee. On examination the child was walking with a limp and the left knee joint was tender and swollen (increase of $1\frac{1}{4}$ inches in size over the right knee). Extension was limited to 160 degrees and flexion to 45 degrees. The temperature over the joint was somewhat increased. The Roentgen-ray showed effusion but no atrophy or destruction. Plaster was applied for 8 days, after which strapping was done, but the condition remained unchanged. Tuberculosis was suspected and the case was referred for aspiration by Dr. M. Herzmark. Twenty cubic centimeters of a pale turbid fluid were recovered. The Wassermann was 4+ in the fluid and blood. For other tests see Table 2. The mother denied venereal infection and her Wassermann was negative. The patient was given mercury ointment locally and injections of bismuth and the swelling subsided within a month. Check up after 8 months showed that the knee remained normal and the blood Wassermann negative.

CASE 3.—D. B., girl, aged 4 years. Her mother stated that the child fell a week previously and developed a swelling of the right knee. The child is normally developed and there were no signs of congenital lues. The tonsils were enlarged and the throat inflamed. The knee was swollen and the central cavity and the suprapatellar bursa were distended with fluid. Only slight limitation of motion existed and there was no increase of local temperature. The Roentgen ray was negative. Thirty cubic centimeters of a pale turbid fluid were aspirated. The Wassermann was 4+ in the joint fluid and the blood. See Table 2 for other findings. The mother had one miscarriage previous to the birth of the child but declined a Wassermann test. Patient was given local inunctions of mercury and referred for general antiluetic treatment. However, this was not carried out and the patient returned after 2 months with the condition unchanged. The right knee was reaspirated and 20 cc. of fluid of the same character were obtained, which again gave a 4+ Wassermann. The patient again failed to carry out the antiluetic treatment for 4 weeks, when she finally returned with swelling and fluctuation of both knees. After 2 injections of bismuth, the right knee improved; however there was increased pain and swelling of the left knee. The patient is still under treatment.

CASE 4.—E. B., colored girl, aged 20 years. She complained of swelling of the right knee since childhood. At the age of 13 the leg was put in a plaster of Paris cast for 4 months; again in 1927 a cast was applied for 9 months. At that time there was also swelling of the left ankle. There was no improvement by the treatment. Since February, 1930, she attended the night Clinic here and was treated with diathermia and massage. The Wassermann in the blood was strongly positive at that time but only physiotherapy was given until September, 1930. The patient was in good general condition. She had strabismus and defective teeth. There were no signs of congenital lues. The right knee was greatly enlarged, the capsule and ligament appearing to be hypotonic. She had marked knock knees. One hundred and twenty cubic centimeters of a greenish, slightly cloudy pale fluid were aspirated on which the Wassermann was 4+. For other findings see Table 2. Mercury was given locally with arsphenamin and bismuth injections. Within 3 months a complete resorption of fluid took place and a check up showed a normal knee after 4 months.

CASE 5.—B. R., colored woman, aged 24 years. She complained of pain and swelling of the right knee for 3 years. She denied knowledge of luetic infection. Her general condition was fairly good but she was constipated. Teeth and tonsils were all right. There was moderate hydrocephalic formation of the skull. She gave no history of serious disease of operation, and denied knowledge of syphilitic infection. The right knee joint was swollen and slightly tender and fluctuated chiefly in the suprapatellar pouch. There was no increase in local temperature. The patient walked without a limp. One hundred and twenty cubic centimeters of a thin, greenish, noncoagulating fluid were aspirated. The Wassermann was 3 to 4+ in the blood and fluid. The Roentgen ray was negative. She was given local mercury ointment and referred for general antiluetic treatment. Due to a misunderstanding she did not appear for the general treatment. She returned a month later, however, with a reaccumulation of fluid and 40 cc. of a turbid, yellow fluid were aspirated. The Wassermann was 2+. For other results see Table 2. The patient was then given 2 injections of novasurol. Gingivitis and uterine hemorrhages appeared; however, the knee joint returned to normal and the blood Wassermann was negative. Check-up examination 2 months later showed a normal knee.

CASE 6.—P., mechanic, aged 38 years, is married, has 2 healthy children. He denied syphilitic infection. Eight months previously he arose suddenly from a chair and felt a snap in the right knee joint, followed by a swelling.

TABLE 2.—FINDINGS IN JOINT FLUIDS IN 10 CASES OF SYPHILITIC ARTHRITIS.*

Case No.	Name.	Age.	Duration.	Diagnosis.	Positive Wassermann.		Cell count.	Neutrophils, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Synovial cells per cent.	Guinea-pig inoculation.	Icterus index.	Remarks.
					Blood.	Fluid.								
1 . .	V. K.	6	2 wks.	Synovitis, bilateral knees	4	4	. . .	66	22	12	0	Not done	3.8	Parenchymatous keratitis 6 weeks before arthritis onset; first aspiration, left knee; second, right knee.
	V. K.	Second aspiration, 1 week later			4	4	18,300	76	16	8	Few	Not done	3.6	
2 . .	C. I.	8	11 wks.	Synovitis, left knee	4	4	. . .	. .	80	5	15	Negative	15.0	Blood admixed.
3 . .	D. B.	4	1 wk.	Synovitis, left knee	4	4	22,500	90	10	. .	. .	Negative	2.0	
	D. B.	Second aspiration 6 weeks later			4	4	5,000	64	28	8	. .	Negative	2.4	
4 . .	E. B.	20	14 yrs.	Synovitis, right knee	4	4	5,450	Few	25	40	35	Not done	2.5	
5 . .	B. R.	25	2 yrs.	Synovitis, right knee	4	3	4,000	20	68	8	4	Negative	2.4	
6 . .	H. P.	38	8 mos.	Synovitis, right knee†	4	4	500	10	70	15	5	Not done	3.2	Hemorrhagic fluid was aspirated from suprapatellar bursa.
7 . .	B. E.	45	2 mos.	Synovitis, right knee	4	4	250	10	85	0	5	Negative	2.1	
8 . .	J. P.	40	6 mos.	Synovitis with juxtartic gumma, left knee	2	2	23,000	84	8	8	0	Negative	2.8	Aspiration after operation.
9 . .	I. D.	8	2 wks.	Osteochondritis, left knee	4	4	10,300	18	52	20	10	Negative	2.8	
	I. D.	Second aspiration			4	3	5,600	60	20	10	20	Negative	Not done	
10 . .	K. A.	27	2 yrs.	Gummatous arthritis, left knee	4	4	. . .	4	81	0	15	Not done	4.0	Ankylosis of left elbow for 3 years.

* Cultures negative in all cases.

† Fluid from popliteal bursa.

The condition persisted in spite of physiotherapy. There was no pain and the patient continued working. He was in good general condition and had had no other serious illness. There were no signs of rheumatic disturbances, nor remnants of luetic infection with the exception of a hydrocephalus and 2 hard nodes over the shafts of the tibia in about the middle of the leg. Roentgen ray showed congenital tubercles of the tibia. The right knee joint was irregularly extended by a bulging in front due to accumulation of fluid in the suprapatellar bursa and a large swelling of the posterior aspect, due to fluid in the popliteal bursa. Both cavities were aspirated by Dr. Saschin. The fluid from the suprapatellar bursa was slightly hemorrhagic. However, as the fluid was not examined until the next day, it cannot be definitely stated whether the blood was not admixed during aspiration. Thirty cubic centimeters of a very pale, thin, only slightly turbid fluid were aspirated from the popliteal bursa. The Wassermann was 4+ in both joint fluid and blood. See Table 2 for other results. The patient was given local inunctions and was advised to take general antiluetic treatment. This he neglected for 4 weeks, at the end of which time he still had swellings, especially of the popliteal bursa. Under antiluetic treatment the swelling disappeared entirely from the suprapatellar and popliteal bursæ.

Case 7.—B. E., laborer, aged 45 years, denied knowledge of venereal disease. For 1 month he had had swelling and pain of the right knee joint and was treated with diathermia and massage without effect. One month later 60 cc. of fluid was aspirated by Dr. D. Sloane. The Wassermann reaction was 4+ in both joint fluid and blood. For other findings see Table 2. The patient was given mercury ointment and general antiluetic treatment. Two months later the knee was practically normal. Seven months later there was recurrence of the effusion which quickly subsided under physiotherapy. The Wassermann was negative.

Analysis. This group represents a late stage of syphilitic infection. Congenital lues may be assumed in the first 4 cases; 3 being children; the joint affection in the 4th dates back to the age of 6 years. The date of infection cannot be ascertained in the remaining 3 cases. The onset was recent in 4 cases (1 week to 2 months' duration), and chronic in 3 cases (8 months to 14 years). The symptomatology is uniform, consisting chiefly of an effusion of the knee joint, bilateral in the first case and unilateral in the rest. In Case 3, effusion developed in the unaffected knee in the course of treatment. The process is almost entirely confined to an inflammation of the synovial membrane. Even the very chronic cases do not present signs of involvement of other joint structure; there is no periarticular thickening nor muscle contracture. The Roentgen ray does not reveal atrophy or destructive or productive changes at the articular surface or metaphysis. For this reason, pain is very moderate; active and passive motion and weight bearing are not markedly limited. Systemic reactions were absent; the temperature was normal; local heat was only slightly raised in the recent cases. The process is eminently stationary, not amenable to nonspecific treatment but still limited to the synovial membrane after years duration.

Diagnosis. First the presence of syphilis and second the syphilitic etiology of the joint affection have to be proven. The history of

infection was negative in this group. However, in 2 cases the mothers had admitted miscarriages, 1 of them having a strongly positive Wassermann. Other signs or remnants of syphilis were missing with the exception of a syphilitic keratitis in the first case. The Wassermann reaction was strongly positive in the blood serum and joint fluids. The diagnosis of syphilis is therefore almost entirely based on serologic evidence. This is sufficient, none of the complications being present which are liable to produce nonspecific reactions.

The second task, the proof of the syphilitic origin of the synovitis, is far more complicated. Jacket and Durand,[15] Reschke,[16] Brunauer and Hess,[14] Schlesinger,[4] Todd,[5] Hoffmann[17] and others found that the Wassermann reaction in the joint fluid was often positive while the reaction in the blood serum was negative. This would indicate a local production of specific antibodies and prove the syphilitic etiology of an effusion. However, the number of cases is limited and the authors did not give details of the technique. Poehlmann,[18] in a careful study, found that the Wassermann reactions in the joint fluids were positive only when the blood was likewise positive.

My own studies[19] and a recent investigation with Dr. Pinkus[20] on the Wassermann reaction in 150 fluids corroborated and amplified these results. It should be emphasized that nonspecific reactions are likely to occur in joint fluids unless a rigid technique is followed. On the basis of these studies we do not accept a positive Wassermann reaction in joint fluids as conclusive proof of the syphilitic nature of the synovitis. However, it is of value as a link in the chain of evidence which is reached by complete examination of the joint fluids, consisting of cultures, gonococcus complement fixation tests, guinea-pig inoculations and cultures for tuberculosis. Positive results of these tests are regarded as evidence against the syphilitic etiology of the arthritis. A negative Wassermann reaction in the joint fluid of a known syphilitic is by itself a proof of the nonsyphilitic etiology of the arthritis.

A positive Wassermann reaction with otherwise negative findings in the joint fluids carries considerable weight in favor of the specific etiology. However, the final decision is still reserved until the progress and therapeutic response confirm the diagnosis.

Interpretation of weakly positive Wassermann reactions must be still more guarded in a case in which infection is denied and other manifestations of lues are absent. Control examinations have to be carried out in the blood and fluid to ascertain the stability of these weak reactions and a prolonged nonspecific treatment should first be given. The failure of this procedure and the success of subsequent antiluetic treatment is the final indication of the significance of the weak Wassermann reactions.

Of other findings in the effusion, the cell count studies do not give differential diagnostic clues. In recent cases the cell count was found to be high, going to 23,000 cells per c.mm., and the polymor-

phonuclears prevailed (up to 90 per cent). In chronic cases the total of cells is low (250 per c.mm.); the polymorphonuclears decrease and the monocytes rise (as high as 90 per cent). In 2 cases the number of synovial cells reached 20 and 35 per cent respectively which, according to my studies,[21] indicates hypertrophic changes of the synovial membrane.

The effusions did contain products derived from the circulation as well as from the hypersecretion of the synovial membrane. This is proven by a peculiar precipitation phenomenon, consisting in the formation of a sack or closed membrane, if a drop of the synovial fluid is let fall into a test tube of diluted acetic or hydrochloric acid. This test and its bearing on the origin of inflammatory effusions is discussed elsewhere.[22]

The importance of bilirubin estimation in the joint fluids will be pointed out in connection with the clinical aspects.

Pathologic evidence is deficient, as in any other form of synovitis. It is not to be expected that the histologic examination will always clinch the diagnosis, because syphilis produces, besides specific granuloma, nonspecific inflammatory pictures. This is brought out by the following reports: Schuchard[23] found in an acute case of syphilitic synovitis, miliary gummata in the subsynovia. Borchard[24] published a case of villus synovitis with gummata. Bosse[25] did an exploratory excision of the synovial membrane in 3 cases and found a granulation tissue in 2 and gumma with giant cells and necrosis in 1 case of hereditary syphilitic arthritis. Bering[26] as well as Hoffmann[17] examined a synovial membrane in 1 case each, finding only nonspecific inflammatory changes. Chesney, Kemp and Baetjer[27] produced syphilitic orchitis in rabbits by injecting joint fluids from 3 cases of luetic arthritis. Unfortunately the experiment was not carried out simultaneously with blood studies; these patients being in the early secondary stage, the possibility that the spirocheta were carried into the fluid from the blood stream is not excluded.

Clinical Consideration. History of trauma was given in 4 patients. That injury was not the direct cause of the effusions is proven by the examination of the fluids. Recent traumatic effusions are hemorrhagic; older effusions have a high icteric index (as pointed out in my recent study on the bilirubin content of synovial fluids[28]). Only once a hemorrhagic fluid was obtained from the suprapatellar bursa; even in this case fluid from the popliteal pouch was free of blood. Therefore, admixture of blood during aspiration must be considered. The icterus index was low, with the exception of 1 case. On the other hand it is well known and confirmed by recent investigation (Michael[29]) that trivial injury may provoke syphilitic manifestations, especially in the late stages of lues. The discrepancy between the history of injury and the inflammatory character of the effusion contributes, therefore, affirmative evidence.

The onset of the synovitis occurred in 4 cases (57 per cent) between the ages of 4 and 8 years. This is significant, as in our material, children up to 14 years amounted to only 10 per cent of the total. In children syphilis is, next to tuberculosis, the most frequent cause of uni- or bilateral arthritis of the knee joints.

Evidence of focal infection was only present in Case 3 where there was a tonsillitis. However, onset after slight trauma, absence of temperature, location, character of the effusion and response to treatment are against a septic or toxic etiology of the synovitis in this syphilitic child.

Therapeutic Evidence. The failure of nonspecific measures in this groups of synovitis is very suggestive. In 5 cases (Nos. 2, 4, 5, 6, 7) internal medication, local applications, physiotherapy, or plaster casts were applied without improvement. The effect of antiluetic treatment is the oldest evidence of the syphilitic nature of a given case of arthritis. James Russel,[30] as early as 1802 recognized venereal contamination as the cause of "one form of symptomatic dropsical swelling of the knee joint, in which the most powerful generic remedies are of no avail, unless the specific disease be first removed by a complete course of mercury." He also made the observation that recurrences happen and it is necessary to continue the treatment until the venereal disease is eradicated. The etiologic evidence is based on the reaction during the course of treatment as well as on the final result.

At the beginning of the treatment either no change nor exacerbation of the symptoms occurred. Of special interest is the first case, which developed the bilateral effusion of the knee joints during a course of antiluetic treatment. This is evidently a Herxheimer reaction, due either to liberated endotoxins or to the effect of the drugs on hypersensitized tissues. The same reaction appears to be responsible for the involvement of the left knee in Case 3 during the treatment. As long as the dosage is insufficient no marked improvement takes place. This is well illustrated in 3 cases (Nos. 3, 5, 6) where the application of energetic treatment was delayed for several months. The effect of the treatment in the intermediary stage can often be demonstrated by the decrease of the strength of the positive Wassermann reaction in the fluids. A full course of treatment is necessary to produce resorption of the effusion, and cure. This result was obtained in 6 cases, the 7th still being under treatment.

Such interpretation of the effect of the treatment eliminates the objections that some of the antiluetic drugs, especially iodids, are efficient also in nonspecific arthritis. Our cases did not receive iodids at all and this drug is not an antiluetic in the strict sense of the word. Iodids are further effective chiefly in the hypertrophic type of arthritis developing past middle age. No evidence was produced that it is of value in simple synovitis. We are inclined to consider the cure of an arthritis in a syphilitic, after insufficient doses of

specific treatment, rather as evidence against the syphilitic nature of the joint involvement. A failure of energetic and prolonged antiluetic treatment in this group, where the process is limited to the synovial membrane, should also be regarded as an indication of a different etiology of the synovitis. If therefore, a latent syphilitic, who has undergone full courses of treatment and is serologically negatives, develops an arthritis, we are quite convinced of the nonluetic etiology of the joint condition. None of our patients had received any antiluetic treatment previously. Recurrences, however, are not to be interpreted as evidence against the luetic etiology, any other manifestation of syphilis being liable to recur. It may indicate rather the need of a new course of treatment.

B. Syphilitic Synovitis with Juxta-articular Gumma.

Case 8.—J. P., colored man, aged 40 years, is married, and his children are healthy. His wife had no miscarriages. He denies knowledge of venereal diseases. For 6 months he had had pain and had noticed a tumor at the outside of the left knee. He is in good physical condition and there are no signs or remnants of lues. At the lateral aspect of the knee joint there was a fibrous tumor about the size of a pigeon's egg. The joint was moderately distended by the fluid, and there was slight limitation of motion. At operation (by Dr. M. Galland) this tumor was found to be connected with the capsule of the joint. The joint cavity was opened during removal. The synovial tissue appeared to be inflamed and hypertrophic, with enlarged villi. About 10 cc. of a yellowish synovial fluid were obtained. The Wassermann reaction was 2+ in the blood and joint fluid. No synovial tissue was removed for examination. The tumor consisted of a yellow, fibrotic tissue. Microscopic slides showed a dense infiltration with round cells, especially perivascularly. There were some epithelioid cells and tuberculoma-like lesions with numerous giant cells. The histologic diagnosis by Dr. Henry L. Jaffé was gumma. After operation, a considerable effusion appeared and 20 cc. of a cloudy fluid were aspirated. The patient was given antiluetic treatment and discharged. For other findings see Table 2.

The diagnosis in this case is chiefly based on the histologic findings of juxta-auricular gumma. The weakly positive Wassermann in the joint fluid and the blood would have needed confirmation by repeated serologic examinations of the blood and joint fluid and a prolonged observation of the effect of both the specific and nonspecific treatment.

C. Syphilitic Synovitis with Osteochondritis.

Case 9.—I. D., a well-developed colored boy, aged 8 years, complained of pain in the left elbow and knee joint for 2 weeks previously. The elbow was normal; the knee was swollen and distended with fluid. Walking was possible without a limp and the pain on motion was only slight. There was no increase in general or local temperature. Sixty cubic centimeters of fluid were aspirated from the left knee. The Wassermann was 4+. Reaccumulation of fluid occurred in 12 days and 40 cc. of greenish, turbid fluid were aspirated. The Wassermann was 3+. For further findings see Table 2. The patient received only local applications of mercury and when he returned 1 month later both knee joints were swollen and fluctuating. The pain was only slight and the patient continued to walk. The blood Wassermann was 4+ and the Roentgen ray showed gouged-out areas at

FIG. 1.—Case 8. Effusion in the right knee joint. Arrow indicates gouged-out area at osteochondral junction of the lateral condyle of the femur, and beginning periostitis.

FIG. 2.—Case 10. Ankylosis of the left elbow. Rarefaction and sclerosis of the articular surface of the humerus (gumma) and periostitis.

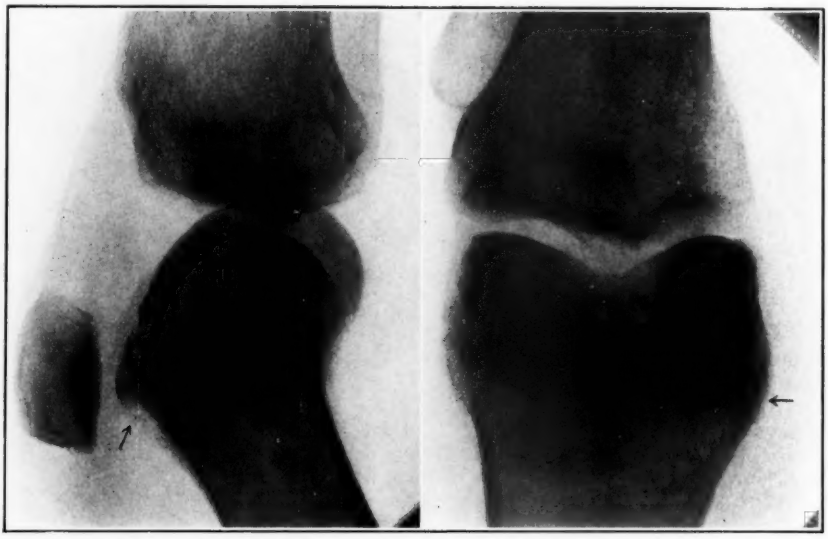

FIG. 3.—Case 10. Effusion in the left knee joint. Gumma at patellar groove of the condyle of the femur (arrow to lateral view) and periostitis (arrow to antero-posterior view).

the osteochondral junction of both condyles of the femur and chondroperiostitis. The patient is now under general antiluetic treatment and the swelling has diminished.

In this case of congenital syphilis, the joint involvement consists of synovitis and early destructive and productive processes of the articular surfaces which are manifest in the Roentgen ray pictures. This strengthens the evidence of the syphilitic etiology; indeed, Dr. Pomerantz, director of Roentgen ray laboratory, made the diagnosis of congenital syphilitic arthritis from the Roentgen ray appearance alone.

D. Syphilitic Synovitis of the Left Knee Joint and Gumma at the Condyle of the Femur. Destruction and Ankylosis of the Right Elbow.

Case 10.—K. A., aged 27 years, in good general condition, denies syphilitic infection. He has had a bowing of the anterior aspect of the tibia since childhood. There has also been pain, swelling and stiffness of the right elbow, which progressed in spite of nonspecific treatment. On examination, the right elbow was found to be deformed and fixed in about 100 degrees of flexion. The Roentgen ray picture showed obliteration of the joint space and bony ankylosis, irregular rarefication and sclerosis of the articular surfaces of the humerus, periostitis at the metaphysis, especially pronounced at the medial epicondyle of the humerus (Fig. 2). The left knee joint was swollen for 1 year. The patient walks with a limp and the knee joint was distended with fluid. Twenty cubic centimeters of greenish, turbid fluid were aspirated. The Wassermann test was 4+ in blood and joint fluid. For other findings see Table 2. The Roentgen ray showed periostitis of the metaphysis and epiphysis of the femur. An area of rarefication and sclerosis is seen at the patellar groove of the femur and at the lateral condyle. The appearance is characteristic of gumma (Fig. 3). There is a small gouged-out area at the chondro-osteal junction of the medial condyle of the tibia. The patient received antiluetic treatment and the knee joint is greatly improved.

The negative history of infection and the malformation of the tibia indicate that this is a case of congenital syphilis. Two stages of a progressive, destructive syphilitic arthritis are presented. The pathologic process in the left knee joint shows chiefly synovitis and gumma at the articular surface of the femur. Although the Roentgen ray appearance is characteristic, involving chiefly only one epiphysis, the diagnosis of tuberculous arthritis was made by 2 radiologists. The older process at the elbow joint illustrates the disastrous effect of the diagnostic error. Here the process has led to destruction and ankylosis of the joint. The importance, therefore, of a careful analysis and complete examination of the joint fluids is reemphasized.

Tabetic Arthropathy. The joint fluid and the blood serum in 1 case gave a negative Wassermann reaction. In another case, not included in this series, both reactions were strongly positive. This fluid was hemorrhagic. These findings tend to confirm the view that the tabetic joint changes are produced by continuous injury and disorganization, due to loss of nerve function. Similar changes are found in traumatic and degenerative cord lesions (syringomyelia).

Tabetic arthropathy should therefore be eliminated as a form of syphilitic arthritis and included in the group of neuropathic arthropathies.

Summary. A well-defined group of syphilitic arthritis with effusions was isolated from the great variety of joint affections attributed to syphilis.

In a series of 112 cases of arthritis with effusion of various etiology and stage, this type of syphilitic arthritis is represented by 9 cases (8.1 per cent).

All occurred in the late stage of infection and at least 5 in congenital syphilis. None of the remaining 4 cases admitted infection; none had received antiluetic treatment.

The knee joint was involved in all cases; no other manifestations of lues were present in 8 cases.

The Wassermann reaction in the blood and joint fluid was strongly positive in 8 and weakly positive in 1 case.

The joint involvement was confined to an inflammatory process of the synovial membrane in 7 cases. One case was complicated by juxta-articular gumma; and another by osteochondritis and periostitis. Finally, 1 case which does not belong to this series presented a destructive form, leading to ankylosis of the left elbow and gummatous arthritis of the left knee joint.

Conclusions. The diagnosis has to establish first the presence of syphilis. In 7 cases this was based on the Wassermann reaction; in 2 cases other manifestations of lues were present (parenchymatous keratitis and juxta-articular gumma respectively).

More complicated is the second task, the proof of the syphilitic etiology of the joint affection. The complete examination of the joint fluid is necessary to rule out other conditions.

The positive Wassermann reaction in the joint fluid, in combination with negative other findings, is the most important evidence. The discrepancy between a history of trauma and the inflammatory character of a joint effusion in a syphilitic is suggestive.

Also the age incidence furnishes some clues, syphilitic arthritis being most frequent in children and young adults. The clinical picture of a monoarthritis or bilateral involvement of the knee joints with only slight degree of pain, muscle spasm, and periarticular thickening without systemic manifestations, is further pertinent.

Roentgen ray evidence is available only when pathological changes have occurred at the articular surface, a condition which was present in 2 of our cases (20 per cent).

The therapeutic evidence is based on the inefficiency of nonspecific and a characteristic response to specific therapy, consisting of no evident change or exacerbation of the type of the Herxheimer reaction after initial doses, and the final success of the full course of treatment, in the cases where destruction of the joint is not too far advanced.

Accurate diagnosis and successful treatment accomplish two results: first they restore the joint; and second they help to eradicate the syphilis.

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ASEPTIC PURULENT MENINGITIS.

REPORT OF SIX BENIGN CASES.

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THE complication of a purulent meningitis secondary to neighborhood suppurative foci in the head or systemic infection is almost always considered to be a grave malignant condition. The occurrence of a series of 6 rather unusual cases of secondary purulent meningitides of benign character with recoveries in all has prompted this investigation of the subject.

There is an extreme paucity of literature upon the subject and we had difficulty in finding cases similar to ours, but we believe there must be a larger number of these cases than the literature would indicate.

In reviewing the literature of benign cases of meningitis other than the epidemic type, we investigated the following author's studies: Mygind[1] reported a series of 210 cases of otogenic meningitis and found 59 cases (28 per cent) recovered. The greatest number of these benign types of meningitis were secondary to lateral sinus thrombophlebitis. Only 10 per cent of the cases that recovered contained bacteria. Those that contained bacteria and recovered were usually streptococcic. Other pyogenic bacteria were more malignant. There are a few other isolated case reports of secondary streptococcic meningitis with recovery although it is common knowledge that streptococcic meningitis has a mortality of about 90 per cent. In the case reports of recoveries there has usually been a removal of the primary focus of infection, *i.e.*, mastoidectomy or lateral sinus drainage with jugular ligation, etc. Huenchens[2] reports such a case. Walthall[3] reported a case of meningitis, similar to ours, secondary to mastoiditis and extra dural abscess that showed a sterile purulent spinal fluid and recovered. Estiu and Lenci[4] report a case of aseptic purulent meningitis of unknown etiology with recovery.

Viets and Watts[5] reported 5 cases of aseptic lymphocytic meningitis, all of which had low spinal fluid cell counts and a symptom complex similar to encephalitis or a meningitic type of poliomyelitis. This in our opinion is an entirely different type of meningitis from

our cases and it is difficult to prove this type as a meningitic clinical entity. Guenther[6] from the Gothenburg pediatric clinic in an extensive article upon this type of meningitis, reported 13 cases of meningitis also showing a lymphocytic reaction in the spinal fluid. In his review of the literature he found about 100 similar cases over a 20-year period. He concluded that these are acute aseptic meningitides of unclear etiology and attempted to establish a nosologic entity. However, he admits they resemble meningitic poliomyelitis or encephalitis. Tuberculosis was excluded because the cases tend to recover.

Quincke,[7] the originator of spinal puncture, established a clinical entity called meningitis serosa. This is an aseptic type secondary to neighborhood or systemic infection, but shows little if any cellular reaction in the spinal fluid. Apparently this type is a toxic meningitis or so-called meningismus.

Baudouin[8] reported an interesting case of aseptic purulent meningitis following cerebral concussion without skull fracture. The case recovered promptly and the author concluded the case was the result of cerebral irritation secondary to the contusion. This case may have been simply meningeal reaction secondary to absorption of small hemorrhage.

Capecchi[9] reported a case of traumatic meningeal apoplexy, complicated by two attacks of aseptic purulent meningitis at monthly intervals, that recovered. He concluded the meningitis was secondary to a circumscribed infection in the neighborhood of the meninges from the skull fracture. This case is similar to Case 4 in our series.

Although the etiology of the purulent meningitis cannot be proved in all our cases, the clinical evidence is strong that in 4 cases the meningitis was secondary to ruptured brain abscesses and in 2 from ruptured cysts. In all cases the spinal fluid was cloudy (purulent) containing a high percentage of polymorphonuclear cells and all were sterile upon culture. One case was apparently of traumatic origin. Spinal drainage was used in all cases except 1 that required the relief of subarachnoidal blockage first by a cerebellar decompression and later by ventricular drainage. The most valuable prognostic criterion has been the sterility of the spinal fluid; namely, absence of bacteria either in smear or culture.

Case Reports. CASE 1.—Ruptured subdural abscess with secondary aseptic purulent meningitis, from sinus disease.

T. A., aged 35 years, married, had an exenteration of the ethmoid sinuses on May 17, 1929, on account of intermittent pain over the eyebrows and was dismissed from the hospital in good condition. On the way home from the hospital (May 20) a sudden upper cervical pain, throbbing and shooting in character, from the occiput to the shoulders developed. The pain increased in severity and was made worse upon head movement and coughing. It was accompanied by vomiting at times. The patient returned to the hospital.

Examination on May 21, 1929, revealed a very sick man, temperature 101° F., with a rigid neck that produced marked pain upon attempted

flexion of the head. All deep reflexes were exaggerated, tremor was present in the hands. Bilateral Kernig's signs were present but focal paralytic signs were absent. The spinal fluid was markedly increased in pressure, containing 1000 cells, with 90 per cent polymorphonuclears per cubic millimeter. Thirty cubic centimeters of fluid was removed and antimeningococcic serum given intracisternally. The smears of the fluid revealed no bacteria, but marked cellular degeneration was present. Repeated cultures on brain broth and blood agar were sterile.

Progress: On the 22d the patient was lethargic, a slow pulse and a partial right third nerve palsy appeared. The blood showed a leukocytosis of 25,300, of which 90 per cent were polymorphonuclear cells. Daily spinal or cisternal drainages were done. By the 25th the pressure was normal and the cell count 230 per c.mm.; on the 21st, 1000 cells and 3000 cells; 22d, 7000 cells; 24th, 900 and the 25th, 230. On the 23d, on account of the right third nerve palsy, a frontal trephine was made on the right side through the frontal sinus. This region was explored subdurally back to the sphenoid region without locating a source of pus. A puncture of the anterior horn of the ventricle revealed clear fluid. The patient left the hospital in 2 weeks, symptom free and has continued in excellent health.

Roentgen rays of the ethmoids showed them poorly visible, the right sphenoid was either not developed or diffusely cloudy.

Comment. This case represents an aseptic purulent meningitis secondary to ethmoid and sphenoid sinusitis and was probably the result of a ruptured sterile subdural abscess. The clinical picture was that of a malignant meningitis at first but repeated spinal fluid studies, with the degenerated type of cells and the absence of bacteria soon revealed the benign character of the pathology.

Case 2.—Ruptured subdural abscess with secondary aseptic purulent meningitis from sinus disease.

Mr. E. R., aged 28 years, single, was admitted to the hospital September 18, 1929. The following history was obtained from the parents. For the past year the patient had suffered from a dull frontal headache, diagnosed as chronic sinusitis. Five intranasal operations had been performed. About 10 days previously the headaches became more severe. On September 16, the headache suddenly became worse, the patient vomited and became delirious. At this time the family physician found a suggestive Kernig reflex, leukocytosis of 24,000 and sent him to the hospital with a diagnosis of brain abscess. During the automobile trip of 300 miles the patient was irrational and violent, and was admitted under the influence of narcotics.

Examination: The patient was very restless and delirious, both optic disks were slightly blurred, marked neck rigidity and bilateral Kernig were present. The reflexes were all hyperactive, no focal paralyses were present. A spinal puncture showed pressure of 30 mm. of mercury. The fluid was purulent containing 3000 cells, 90 per cent of which were polymorphonuclear cells, but no organisms were found in the smear. The protein content was 45 mg. per 100 cc. The fever ranged from 100° to 102° for 17 days; pulse, 64 to 100; the blood leukocytes, 18,700, of which 88 per cent were polymorphonuclears.

Head Roentgen ray study demonstrated the frontal sinuses as pneumatic. The right ethmoids showed some haziness in outline. The posterior ethmoids appeared to be broken down and the area represented by thickened membrane. The posterior sphenoids on the left were well visualized. It was the opinion of the roentgenologist that the ethmoids had been the seat

of previous infection, the brunt of which had been carried by the left middle ethmoids.

Progress: On the 19th the severe headache continued, the patient was in stupor, involuntary muscular twitchings were present, but no focal neurologic signs were present. The spinal fluid under 14 mg. of mercury pressure was less turbid, the cell count was 1000 per c.mm. The cultures of the fluid were all sterile. Spinal drainage was continued daily with a gradual clearing up of purulency; after about 4 weeks the patient was discharged from the hospital, continuing to feel somewhat weak and suffering from headache which gradually lessened in severity. At the present time the patient is symptom-free, working and apparently in normal health.

Comment. This case was very similar to Case 1, namely, secondary purulent meningitis from ethmoid sinusitis with a probable intermediary stage of subdural abscess with final rupture producing a sterile meningitis. Again repeated spinal fluid studies revealed the benign character of the disease which at first seemed malignant.

CASE 3.—Staphylococcic bacteremia, multiple body abscesses, sinusitis, osteomyelitis of frontal bone, left frontal lobe abscess with recurrent attacks of purulent aseptic meningitis.

Mrs. G. T. D., aged 25 years, was first admitted to the University Hospital on August 7, 1925, with symptoms and findings of acute left frontal and ethmoid sinusitis. The examination was negative except for a markedly swollen left eye, bilateral optic neuritis, fever and leukocytosis. Head Roentgen ray showed extensive left frontal osteomyelitis. On August 8 and 15, sinus operations were performed on the frontals and ethmoids. On August 21 a breast abscess was drained and on the 26th an abscess was opened in the region of the right hip. At this time the patient was very toxic and at times was irrational. The blood culture was positive for staphylococcus aureus. In November intracranial pressure symptoms appeared in the form of stupor, increasing headache, and vomiting. Right-sided pyramidal tract signs were present. On November 25 a trephine was made by Dr. J. J. Keegan, through the left frontal sinus region and a brain abscess was drained from the left frontal lobe. About 1 ounce of pus was removed from which a pure culture of staphylococcus was cultured. The patient continued to run a stormy course; from the onset fever was constantly present as high as 105° F. for 60 days. On January 7, 1926, there was considerable cortical herniation with sloughing tissue. On January 28, 1926, this herniation was cut away and a large sequestrum was removed from the orbital plate. Blood cultures were positive for staphylococci on 2 occasions, the leukocytes were usually high from 24 to 30,000. On February 11, 1926, the patient was dismissed from the hospital in fair condition.

The patient was readmitted on June 26, 1928, on account of recurrent cerebral symptoms in the form of right-sided convulsive seizures, attacks of aphasia, stupor and fever, with temperature of 105° F. Signs of meningitis were present. Daily spinal punctures were performed. The fluid was cloudy and under markedly increased pressure with cell counts ranging from 200 to 3000, of which 90 per cent were polymorphonuclear cells. All specimens were sterile to culture upon a number of different media. The left frontal region was again explored and more pus was drained. The patient left the hospital in fair condition in about 3 weeks' time.

On October 15, 1928, the patient was again readmitted in a critical condition on account of the same symptoms present in June. At this time the spinal fluid was again 20 to 22 mm. of mercury pressure, turbid with polymorphonuclear cells from 500 to 1000 per c.mm. All cultures of the spinal

fluid were again sterile. Double choked disks of 4 diopters were present. On November 20, the patient was again explored in extremely critical condition and about 1 ounce of creamy pus drained from the frontal lobe. A stormy convalescence followed with recurrent attacks of meningitis. On December 4, when the spinal fluid contained 4000 cells per c.mm. only about 5 cc. of fluid could be drained, the condition suggesting a block of the foramen magnum. The spinal fluid cultures were still sterile, but each culture from the brain abscess contained staphylococci and at one time some streptococci. The fever was high, up to 104° F. for 35 days. On the 88th day the patient was again dismissed in fair condition.

The patient returned again for a few days' observation in 1929 on account of a psychoneurotic upset. In 1930 she went through a normal pregnancy and has shown no other evidence of return of the infection. The patient was reëxamined in March, 1931, on account of occasional convulsive seizures. An encephalogram showed moderate hydrocephalus and extensive arachnoiditis, especially over the left frontal lobe. She probably will continue to suffer from symptomatic epilepsy.

Comment. This patient represents an interesting type of recurrent sterile purulent meningitis secondary to chronic brain abscess. The etiology was sinusitis complicated by osteomyelitis and a staphylococcemia. It seems an accident that this patient recovered, as the disease was always of malignant character. By the time the cerebral complications occurred the patient's immunity was high or the organisms reduced in virulence. It is interesting that organisms were easily cultured from the brain abscess but could never be demonstrated in the spinal fluid.

Case 4.—Head trauma followed by two attacks of cerebrospinal fluid block, ruptured brain abscess with purulent aseptic meningitis.

Mr. H. A., aged 20 years, when first examined on April 26, 1925, gave the following history: On February 16, 1924, the patient slipped and fell upon icy ground striking the occiput on a tree. He got on his feet immediately, walked 3 blocks then fell unconscious. He remained unconscious for 4 hours. Upon coming to, the patient suffered severe pain in the occiput and back of neck and felt nauseated. After 1 week's osteopathic treatment the patient felt well and returned to work.

Several days later upon stooping he noticed a headache, which continued with exacerbations upon effort or hard work. In March and April, 1925, the headaches became more intense and at times were accompanied by vomiting.

At the examination on April 26, the patient was groaning with pain, pulse rate 46. The facies were flushed, retracted rigid neck and double choked disks were present. An acute cerebrospinal fluid block was obviously present. The patient was taken to the hospital immediately. Dr. J. J. Keegan performed a suboccipital decompression. The dura was very distended and the arachnoid appeared thickened. A tentative diagnosis of arachnoiditis was made. Later events indicate that the condition was entirely a pressure phenomenon.

Following the operation the acute pressure symptoms subsided, the neck rigidity remained for several weeks before subsiding.

Reëxamination on May 23, 1925, showed no objective neurologic findings, although the patient still complained of some headache and dizziness. On August 23, 1925, the neurologic examination was negative; the patient was doing light work and felt well.

On December 5, 1925, the spinal fluid was under 16 mm. of mercury pressure. The cell count, protein content, Wassermann and Lange tests were negative. The patient complained of dizzy spells. Outside of the increased spinal pressure reading the examination was again negative.

In February, 1926, another examination was normal, the spinal pressure was 12 mm. of mercury. On August 23 the patient was hospitalized again for spinal puncture. The physical and neurologic examinations were normal. The spinal pressure was 10 mm. of mercury. A few hours following the puncture, the patient complained of sudden severe head pain, and vomited. The temperature was 101° F., pulse 55 to 65, the head was retracted, neck rigidity and bilateral Kernig were present. The findings were those of an acute cerebrospinal fluid blockage. Dehydration treatment was ineffectual. A ventricular puncture was done and 45 cc. of purulent spinal fluid was removed which contained 3200 pus cells per cubic millimeter. No organisms were found on smear and the fluid was sterile to culture. Following the ventricular drainage the patient's condition improved, the fever gradually subsided and the leukocyte count of 22,000 became normal. The patient was dismissed in fair health on August 31, 1926. The diagnosis was ruptured sterile brain abscess with secondary aseptic purulent meningitis.

The patient has been reëxamined at frequent intervals since that time but he has not shown any symptoms of recurrent trouble. At present he is working and apparently in normal health.

Comment. In this case the primary etiology is difficult to explain. The entire symptom complex apparently began with the head trauma. The most logical explanation for the purulent meningitis was a ruptured sterile cerebral abscess. The nature of the abscess formation is difficult of explanation. The abscess ruptured into the ventricles rather than into the subarachnoid space. The abscess produced 2 attacks of foramen magnum blockage which required first a cerebellar decompression and later a ventricular drainage for relief. The final rupture of the abscess was possibly produced by a spinal puncture. The meningitis, although purulent was again of aseptic character as shown by absence of bacteria.

We have recently observed another interesting case of cerebral abscess that followed a stab wound in the frontal bone about 14 years ago. The abscess ruptured while the patient was under observation in the hospital. The resultant meningitis was not entirely aseptic as organisms were cultured upon one occasion, after 72 hours' incubation. In spite of the relatively benign character of the meningitis the patient died. The necropsy revealed the traumatic abscess entirely evacuated. There still remained some fibrinopurulent exudate in the subarachnoid cisterns. There was no cerebral edema and the brain sections were normal. The cause of death was obscure. We have not included this patient in our series because the meningitis was not entirely aseptic. The clinical picture was similar to Cases 1 and 2 and the meningitis was of benign type. The bacteria found were not of virulent type and could only be demonstrated with great difficulty.

CASE 5.—Ruptured brain cyst with recurrent attacks of aseptic purulent meningitis.

R. H., aged 7 years, was first seen November 7, 1927. The history dated from October, 1925. The onset began with spells of headache and vomiting. In November, 1925, the patient complained of diplopia and amblyopia. In December, 1925, the mother noticed convulsive twitchings of the left side of the face and the head was drawn backward. The family physician found a fever of 100° F. and signs of meningitis. A lumbar puncture revealed turbid fluid. About 40 cc. were removed, some questionable extracellular diplococci were found, none intracellular. Two punctures daily were done for 3 days when the fluid cleared and the patient was able to be up within 10 days.

In January, 1926, when the patient was taken to a large clinic, where a very complete neurologic examination was done, only double choked disks were found. Complete laboratory studies including spinal fluid tests and Roentgen ray examination of the head were made with negative findings. The diagnosis was some obscure inflammatory disease with residual hydrocephalus, with a possibility of a brain tumor in a stage of remission. In June, 1926, the patient again became worse, losing the vision in the right eye within a few days and developing fever and headache. Some fever continued off and on during that summer. In August, 1926, the vision in the left eye diminished and the patient returned to the clinic. At that time the neurologic examination disclosed generalized pallor of both disks without swelling. There was an absolute sector defect in the right eye continuous with the blind spot and there was no central fixation in that eye. The vision was moving objects in the right and 6/15 in the left. It was suggested that the type of field seen was not that usually found with a secondary optic atrophy following choked disk. The remainder of the neurologic status was normal, the spinal fluid was again normal. The opinion was still held that the condition was primarily inflammatory in the absence of pressure phenomena. After returning home the patient was in fair condition until December, 1926, when he contracted pertussis and right otitis media. Renewed headache and vomiting followed. In January, 1927, the family physician again found turbid fluid with thousands of polymorphonuclear cells but sterile to culture, spinal drainages were continued for 2 weeks when the fluid again cleared. Frequent spinal punctures were done from then on to relieve headache. On one more occasion purulent spinal fluid was obtained.

On November 8, 1927, our neurologic examination showed marked atrophy of both optic disks, apparently secondary to papilledema. The vision in the right eye was central with the right half entirely gone and a narrow band of vision in the left half of the right field extending horizontally from the fixation point. The remainder of the examination was negative. Lumbar puncture showed 12 mm. of mercury pressure, 8 cells per cubic millimeter and normal protein content. Severe head pain followed the puncture. Roentgen rays of the cranium showed an area of increased density in the right temporal area close to the sagittal plane approximately $1\frac{3}{4}$ inches in diameter, suggesting a deposit of calcium or dense fibrous tissue. There was an excavation of the sella turcica with partial obliteration of the sphenoidal sinus and some erosion of the posterior clinoid process. Diagnosis: suprasellar craniopharyngeal pouch cyst was made upon the Roentgen ray.

A right temporal trephine was done by Dr. J. J. Keegan. A small opening was made through the dura, which was very tense. A trocar needle was inserted directly inward. At a 4 cm. depth a cyst was struck and about 3 ounces of thick yellow fluid containing crystals were removed.

The patient improved and returned home, but continued to have intermittent attacks of purulent meningitis and died in an attack several months later.

CASE 6.—Ruptured meningocele producing aseptic purulent meningitis. Baby M. F., aged 7 weeks, was admitted to the hospital August 5, 1928. The patient was born with a lumbosacral tumor (meningocele), but had been in normal health until 5 days previously when it developed numerous generalized convulsions and stupor. The examination revealed only a bulging anterior fontanelle and a fever from 90° to 103° F. that persisted for 1 week. Cisternal puncture revealed a turbid fluid, containing 760 cells per cubic millimeter with shreds of fibrin; about 50 per cent of the cells were polymorphonuclear leukocytes. The protein content was 15 mg. per 100 cc. and Lange 2233210000. On August 8, a leukocytosis of 15,000 was present. On August 13 the cisternal fluid was yellow under increased pressure and contained 1500 cells per cubic millimeter, 60 per cent of which were polymorphonuclear cells. Epithelial cells and débris in the smear suggested that it had a lining membrane. On September 1, 1928, a lumbrosacral Roentgen ray showed a fairly good development of the vertebral segments and their spinous processes down to the fourth and fifth lumbar and first sacral. The first sacral demonstrated a relatively poor development of its posterior structures.

Operation by Dr. J. J. Keegan. There was no external ulceration. A longitudinal incision was made on each side meeting at the upper and lower angles, by blunt dissection. A narrow neck of a sac was disclosed about 7 mm. in diameter and was freed from the skin. An incision in the inferior wall of the tumor cavity showed obliteration by grayish tissue. The neck was tied with silk as low as possible and the tumor removed. No fluid escaped and there was no pressure on the stump. The defect in the spine was less than 1 cm. in diameter and no plastic closure was thought necessary so the skin was closed. On September 9, a cisternal puncture showed 18 cells per cubic millimeter. The baby made a normal recovery with normal motor and sensory functions in the lower extremities. The child has continued to develop normally in every respect.

Comment. Cases 5 and 6 are meningitides of slightly different origin from the other 4. They are both secondary purulent aseptic types secondary to ruptured cystic contents into the subarachnoid space. Case 5, a recurrent rupture of a craniopharyngeal pouch cyst, produced attacks of purulent meningitis in which the etiology was unknown for some time. This case illustrates the extreme difficulty in certain cases of intracranial compression in children of differentiating inflammatory from neoplastic disease. Although the patient of Case 5 finally died, the individual attacks of meningitis while purulent were essentially benign or sterile aseptic reactions. Case 6, a babe of 7 weeks, had meningitis secondary to ruptured cystic contents from a meningocele, with complete recovery both from the meningocele and the secondary meningitis.

Summary. A review of the literature upon the benign types of purulent meningitis was made and only a few scattered reports could be found.

Six cases of purulent meningitis have been observed, 4 of which were secondary to ruptured brain abscesses. These abscesses were

probably sterile at the time of rupture. All cases recovered and all the spinal fluid cultures were sterile. In 2 cases the apparent etiology of the presumed subdural abscess was chronic sinusitis. In 1 other case the abscess (intracerebral) was secondary to frontal sinusitis that had also produced a metastatic pyemia. In 1 case the etiology was not clear, but it was presumed that an intracranial abscess developed posttraumatic, finally rupturing into the ventricles. In 2 cases puriform meningitis followed ruptured cysts, 1 a brain cyst and another a ruptured meningocele.

The most valuable diagnostic guide was the spinal fluid studies. In some cases, cellular degeneration, débris and atypical cells were present that suggested a lining membrane from abscess or cyst. This observation gave a clue that the meningitis was secondary to ruptured tumor. In all cases the absence of bacteria upon repeated smear and culture studies indicated a benign or sterile type of inflammation.

Spinal drainage was the most important single therapeutic procedure. In 1 case pressure complications required decompression and ventricular drainage.

We believe that this type of benign meningitis is more common than the literature review would indicate and may account for some reported recoveries of types that were presumed to be of malignant character.

In our opinion the etiologic factor of secondary meningitis from ruptured brain abscess should be more frequently considered in a differential diagnosis of atypical meningitides. Vigorous spinal drainage should be instituted in cases of secondary meningitis in the hope that the infection is benign.

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SPASMODIC TORTICOLLIS: RESULTS OF REMOVAL OF FOCI OF INFECTION AND TREATMENT WITH SPECIFIC VACCINE.*

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Between January 1, 1910, and January 1, 1929, 534 patients suffering from all types of torticollis were admitted to The Mayo Clinic. For this study patients who had suffered from the spasmodic type of torticollis and who had received medical treatment were considered. Patients suffering from other types of torticollis and all of those who had undergone orthopedic or neurologic surgical procedures were not included in this study. Thus, there were left for our study 247 patients to whom letters of inquiry were addressed and from whom we obtained 100 replies. These were carefully studied, and 18 were excluded because of insufficient data, the death of the patient (in no instance attributable to torticollis) or because the patient presented associated neurologic disturbances.

Of the 82 patients who remained 39 were women and 43 were men. The average age of the patients at onset of the condition was 39 years; their average age at the time of admission to the clinic was 44 years; the average duration of symptoms prior to their admission to the clinic was 5 years. The average duration of symptoms of patients who continued to suffer from torticollis at the time of this inquiry was 12 years. Those patients who reported complete disappearance of all symptoms had had their symptoms for an average of only $3\frac{1}{2}$ years.

At the time of the inquiry 44 patients (54 per cent) had not improved, 16 patients (19 per cent) were entirely relieved of the torticollis and 22 patients (27 per cent) reported improvement. It is difficult to evaluate the group listed as having "improved" for this is purely the patient's personal opinion. We have, therefore made no effort to separate this group into degrees of improvement. In some aspects of the study we were interested in knowing in how many cases the torticollis was stationary, and in how many there was improvement, either partial or complete. In such instances the cases in which the condition had improved and in which it had disappeared were listed together.

Removal of foci long has been advocated as an essential part of treatment. In determining the results which followed removal of foci of infection it is necessary to know whether the patient for

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whom removal of foci was advised had followed the advice. Fifty-four of 58 patients who had been advised to have teeth removed followed the advice; 4 did not. Five of the 21 patients who were advised not to have teeth extracted followed the advice; the other 16 of these 21 did not state whether they had had teeth extracted. In 3 cases it was not stated what the advice had been concerning extraction of teeth, nor did the patients state what course they had followed in this respect. Thirty-seven of the 42 patients for whom tonsillectomy was advised underwent the operation; 5 did not. Of the 33 patients for whom tonsillectomy was not advised 1 had the tonsils removed, 17 of the 33 did not (in 11 of these 17 cases tonsillectomy had been done before the patients were admitted at the clinic), and 15 of the 33 did not state whether or not they had had their tonsils removed. In 7 cases it was not stated whether or not the patients had been advised to undergo tonsillectomy and the patients did not state whether or not they had undergone the operation.

In Table 1 is a comparison of the number of patients for whom tonsillectomy and removal of teeth, either or both, was advised. Thirty-five patients gave evidence of focal infection in both teeth and tonsils. In only 1 instance was focal infection elsewhere in the body found and treated; this patient had a nonspecific infection of the prostate gland.

TABLE 1.—CASES IN WHICH REMOVAL OF TEETH AND TONSILS, EITHER OR BOTH, WAS ADVISED.

	Infected teeth.			
	Extraction advised.	Extraction not advised.	Not stated.	Total
Infected tonsils:				
Removal advised	35	7	..	42
Removal not advised	23	10	..	33
Not stated	..	4	3	7
Total	58	21	3	82

In Table 2 the cases are listed as to whether foci of infection were removed. The table notes, furthermore, whether, on the one hand, torticollis had remained stationary, or, on the other, whether it had disappeared or improved. There was a difference of 15 per cent in the improvement or disappearance of the torticollis in favor of removal of foci. There are, of course, factors which might affect the validity of this difference of 15 per cent. The largest factor is the possibility that this may be merely a sampling difference; in other words, that a similar group of 82 patients might not reveal this difference. Using the Chi square theory of determining the probable significance of the difference between proportions, it is found that there are 79 in 100 chances that this is a difference greater than would arise from sampling. In order to have a 96 per cent chance of this difference of 15 per cent being absolutely valid, it

would be necessary to have a series of 221 cases. Although we are unable to determine with absolutely certainty that this is a significant difference, yet we have reasonable grounds for the assertion that the difference between 51 per cent improvement or cure after removal of foci and 36 per cent without removal of foci is of sufficient significance to warrant continuance of this procedure.

TABLE 2.—IMPROVEMENT AND LACK OF IT IN RELATION TO REMOVAL OF FOCI AND CONTINUED PRESENCE OF FOCI.

	Condition of torticollis.			Per cent of patients improved or cured.
	Stationary.	Improved or disappeared.	Total.	
Foci of infection removed	28	29	57	51
Foci of infection not found or not removed	16	9	25	36
Total	44	38	82	46

The other form of treatment most commonly advised was the use of specific vaccines.

TABLE 3.—IMPROVEMENT AND LACK OF IT IN RELATION TO ADEQUATE, INADEQUATE AND NO TREATMENT BY SPECIFIC VACCINE.

	Condition of torticollis.			Improved or disappeared (per cent).
	Unimproved.	Improved or disappeared.	Total.	
Adequate specific vaccine therapy	9	6	15	50.0
Inadequate or no specific vaccine therapy	35	32	67	47.8
Total	44	48	82	46.0

In Table 3 we have listed all cases in which vaccine was given and the condition of the torticollis. We have arbitrarily defined as a satisfactory trial of vaccine the administration of vaccine for a period of at least 3 months. In every instance this vaccine was prepared at The Mayo Clinic. It is found that in 40 per cent of this group of cases the torticollis improved or disappeared, as compared to 47.8 per cent in cases in which no specific vaccine treatment was given or the period of treatment was inadequate. According to the Chi square theory of determining the probable significance of the difference between proportions, there are 58 in 100 chances that this is a difference which might arise as a sampling process. That is, these percentages might be reversed were 82 other patients with torticollis similarly studied. Therefore, conclusions cannot be drawn from this difference of 7.8 per cent. As Rosenow has said: "The benefits which follow the removal of foci proved to contain organisms and the use of autogenous vaccine, although often striking, do not occur regularly enough to prove etiologic relationship."

Table 4 is included only because it is of interest to know to what cause the patients attribute their disability. It is self-explanatory,

and because it is based entirely on the patient's ideas and not on any scientific study or clinical impression, conclusions are not drawn from it.

TABLE 4.—PATIENT'S OPINION AS TO CAUSE OF TORTICOLLIS.

Patient's opinion of cause.	Condition of torticollis.			
	Stationary.	Disappeared.	Improved.	Total.
Nervousness, worry, overwork, etc. .	10	7	5	22
Focal infection, exposure, etc. . .	6	7	4	17
Trauma	7	..	7	14
Not stated	21	2	6	29
Total	44	16	22	82

It is also of interest to know to what procedure the patients attribute their improvement. Twenty-eight of the 38 patients in whom the torticollis disappeared or improved answered this question. Twelve gave credit to rest and relaxation, 5 to removal of foci, 2 to osteopathy, 2 to patent medicine and 1 each to vaccine, vaccine and rest, thyroidectomy, medicine, Christian Science, removal of foci together with chiropractic and chiropractic alone. The character of this information again precluded the possibility of drawing any conclusions from it.

Summary. A study has been made of 82 patients who had received medical treatment for spasmodic torticollis. Thirty-nine of the patients were women and 43 were men. The average age at onset was 39 years, the average age at admission to the clinic was 44 years and the average duration of symptoms prior to admission to the clinic was 5 years. The average duration of symptoms of those patients who continued to suffer with torticollis to the time of this inquiry was 12 years. Those patients who reported complete disappearance of all symptoms had had symptoms for an average of only 3½ years. Forty-four of the 82 patients (54 per cent) were not improved; 16 patients (19 per cent) reported complete disappearance of symptoms; 20 patients (27 per cent) reported improvement. The patients coöperated well when advised to have foci of infection removed. Fifty-one per cent of the patients who had foci of infection removed reported improvement or disappearance of the torticollis, as compared to 36 per cent of those who did not have foci removed. This difference of 15 per cent is considered to be of sufficient significance to support the belief that removal of foci is warranted.

Conclusions cannot be drawn from this series as to the value of specific vaccine treatment for spasmodic torticollis.

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THE CLINICAL CYCLE OF GOITERS.

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Clinicians and pathologists are still describing their findings in the stages of goiter transformation as representing certain distinct types of goiter. Attempts have been made during the last three generations to make the clinical and histopathologic pictures of goiters coincide; but as much confusion still exists as originally, and it would seem that the problem should be approached from a different angle.

The more one studies patients suffering from thyroid enlargements, and tries to correlate the clinical and pathologic findings, the more he finds that there are many discrepancies between the two, and to consider the types as clinical entities is frequently misleading. There have been a few observers during recent years who have maintained that the types of goiter as merely representing stages of a continuous disease process. Hertzler[3] was one of the first to teach this, as he had observed the life cycle of his patients, and had not confined his observations to the signs and symptoms at a given period of the disease. In previous publications[4,5] I have reported cases to prove that these different types do not represent clinical entities. Boyd,[1] in his recent addition on surgical pathology, states: "Goiters are usually divided into three main groups, which are regarded as being entirely distinct entities. The first is known as simple or endemic (colloid) goiter, the second as adenomatous, the third as exophthalmic goiter. With the exception of the second, these names are purely clinical and have no pathological connotation. The second is certainly pathological, but it is unjustified for the nodules are not adenomata in the pathological sense."

Keilty,[7] in an article based on the pathologic study of 1000 thyroid glands, states: "Following the combined study of histories, gross specimens and microscopic slides over a period of 10 years, the opinion is expressed that a large proportion of nodular thyroid glands, toxic and nontoxic, show the pathological evidence of chronic productive, and contractive thyroiditis rather than of adenoma."

The following cases will serve to illustrate the confusion that still exists if one tries to pigeon-hole the diagnosis from the findings at certain stages of the disease.

Case Reports. Case 1.—A female, aged 17 years, was admitted to the thyroid clinic on July 17, 1930, complaining of enlargement of her neck.

Patient first noticed enlargement of the neck at the age of 9 years, at which time she was treated by her family physician for 1 year and later in this institution for several months with iodin and thyroid medication, but noticed no improvement and discontinued treatment. For the past 4 years her neck was gradually enlarged, but she has no other complaints. Examination revealed nodular enlargement of the thyroid in both right and left lobes, the neck measuring 33 cm. and basal metabolism −8 on July 14, with all other laboratory work negative. Diagnosis of bosselated goiter was made, following Hertzler's teaching, or if one uses the accepted classification, a diffuse adenomatous goiter. Patient was put on thyroxin, $\frac{1}{60}$ gr., intravenously, every 2 weeks, and thyroid extract, 2 gr. t. i. d. by mouth. She has shown marked improvement under medical treatment, and at this time the enlargement has diminished 75 per cent. This case represents a type of goiter that is frequently operated upon, while in reality the nodules were produced by the connective tissue formation in the gland.

Case 2.—A female, aged 17 years, was transferred to our clinic December 18, 1930, having been treated in another clinic in the hospital for 7 years. She complained of enlargement of her neck, which was getting worse. Patient had been treated at the Post-graduate Hospital for 7 years, taking iodin and thyroid extract. At the time of her admission a diagnosis of adolescent goiter was made, and although she has been under continuous treatment a lump was noticed in the region of the isthmus about 2 years previously, which has gradually enlarged. Basal metabolism was −6 on December 16, 1930. Patient has been on iodin and thyroid medication since entering our clinic without any improvement; diagnosis of adenoma of the isthmus being made which will necessitate an operation. This patient, although under continuous observation for 7 years, developed an adenoma while being successfully treated for an adolescent goiter.

Case 3.—Female, aged 39 years, was admitted to the thyroid clinic February 5, 1931, complaining of nervousness and loss of weight for 2 to 3 months. Past history negative. Patient has been well until 2 or 3 months before admission when she gradually began to decline and has been losing weight, estimated at about 20 pounds. She has become extremely nervous and has palpitation of the heart, also enlargement of her neck and prominent eyes. Examination revealed exophthalmos, enlargement of the thyroid with a thrill over the gland and pulse 140, her basal metabolism rate being +64 on February 15, 1931. Patient was advised admission to the hospital and was put on iodin and sedatives for 3 weeks before being operated upon. A one-stage thyroidectomy was done on March 4, 1931. Pathologic findings revealed Basedow's disease with included fetal adenoma. Although this patient gave a relatively short history, the pathologic study revealed an exophthalmic goiter with an adenoma which could not be detected on physical examination.

Case 4.—A female, aged 64 years, was admitted to the thyroid clinic September 11, 1930, complaining of enlargement of her neck and difficulty in swallowing for the past few years. Patient states she had the enlargement of her neck since a young girl, at approximately the age of 16 years, and this has gradually become larger and about 10 or 15 years ago she noticed irregular nodules in her neck which have enlarged gradually and at the present time she has difficulty in swallowing and breathing. Examination reveals definite nodular masses in both lobes of thyroid. Roentgen rays of the chest on September 26, 1930, revealed a deviation of trachea and esophagus to the left with calcification of the lower poles of the thyroid. Basal metabolism was −1 on September 25, 1930. A diagnosis of calcified adenomata of the thyroid was made. The patient was operated upon on October 10, 1930, and the pathologic report revealed an adenocarcinoma of the thyroid with extensive calcification.

These cases represent what is routinely found in any clinic dealing with thyroid diseases if careful histories are taken, and the clinical and pathologic findings are correlated. Other cases could be cited to illustrate that the apparent types of goiters are interchangeable, if one follows the patient for a sufficient length of time or gets an accurate history.

Comment. It is difficult for one to believe that the thyroid gland could develop in itself colloid, adenomatous and exophthalmic goiters which are clinically and pathologically distinct entities; also chronic thyroiditis, Riedel's struma and Hashimoto's disease, which represent different pathologic entities. In clearing up any misunderstanding that exists in the pathologic study of this disease, it is essential to have a clear conception of the normal histology for the different periods of life, from stillbirth to senility. In a study[6] of people meeting with accidental death from stillbirth to over 80 years of age, it was found that the normal histologic picture varied greatly for people of relatively the same age, and it is difficult to draw conclusions as to what constitutes normal thyroid histology. This being so, it is even more difficult to classify the abnormal.

When we come to consider thyroid diseases we have to admit a dysfunction of the gland, which is first manifested by colloid deposits during adolescence or in later life. Sometimes this stage of the disease responds to medical treatment, while on the other hand the enlargement may spontaneously disappear. If there is an accompanying chronic thyroiditis for a number of years, which may vary greatly in severity, the connective tissue which is produced by this process will ultimately produce nodules, or so-called adenomatous goiter, while on the other hand the patient may develop an exophthalmic goiter before the nodular stage is reached. It is difficult, and sometimes impossible, to palpate a thyroid enlargement in a typical exophthalmic goiter, so how can we say that there has not been a colloid disturbance preceding the exophthalmic goiter which was never detected by the patient, or by the family physician?

In considering chronic thyroiditis, Riedel's struma and Hashimoto's disease, one is confronted with trying to place these types of disease in the cycle of pathologic changes. Graham and McCullagh,[2] after a most thorough study of 4 cases of Hashimoto's disease, state: "An acceptable explanation of the pathogenesis of the changes in the thyroid is not apparent. It would be simple enough to follow the line of least resistance and agree with one of the prevailing views, *viz.*, that struma lymphomatosa is the early stage of Riedel's struma. A review of the literature and personal experience with both types of lesions have inclined us to the view that they are quite dissimilar. Riedel's struma more nearly approaches a true inflammation than dose the lesion described by Hashimoto's." As the other types of goiter are now being con-

sidered as stages of a continuous disease, it may be that ultimately chronic thyroiditis, Riedel's struma and Hashimoto's disease will be proved to be of an inflammatory nature and the difference in the findings will be due to the response to the infection.

Conclusion. From a clinical point of view it would be much simpler for us to regard the different goiters as stages of a continuous disease process and treat all cases medically unless hyperthyroidism, pressure symptoms or an encapsulated tumor actually exists. In this way some of the nodular goiters that are called adenomata would be found to be colloid rests from connective tissue formation, and these will in turn respond to iodin or thyroid medication, thus saving many needless operations.

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REVIEWS.

ELECTROTHERAPY AND LIGHT THERAPY. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, Polyclinic Medical School and Hospital, New York. Pp. 528; 211 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $6.50.

THE preface states that this volume had its conception in the conviction that practising physicians should be shown the possibilities and limitations of that part of modern physical therapy which they themselves can carry out in their own offices. There is no doubt that physical therapy has been largely accepted as an integral part of the practice of medicine and surgery. This book should prove useful not only to the physician who actually practices electrotherapy and light therapy as a specialty, but it should be equally valuable to the practitioner who wishes to gain information as to what is being done in this field of treatment. The Reviewer would particularly invite attention to the several brief but excellent chapters on Electrophysics and on Photophysics. B. L.

A TEXTBOOK OF NEUROANATOMY. By ALBERT KUNTZ, PH.D., M.D., Professor of Microanatomy in St. Louis University School of Medicine. Pp. 359; 197 illustrations. Philadelphia, Lea & Febiger, 1931. Price, $5.50.

THIS book has been written to aid the student in his first attempts to gain some knowledge of the anatomy and physiology of the nervous system. The author bases his presentation on the assumption that the fundamental plan of structure is relatively simple, though the anatomical structure is somewhat intricate. The subject is considered in twenty-two chapters, of which four, comprising nearly one-quarter of the book, are devoted to the cerebral hemispheres. The illustrations of actual tissues are derived from a variety of sources, and there are many diagrams of the courses of tracts. At the ends of the chapters are lists of references to the literature which will be useful to the student seeking further information. W. A.

THE TREATMENT OF ASTHMA. By A. H. DOUTHWAITE, M.D., F.R.C.P. (LOND.), Assistant Physician, Guy's Hospital. Pp. 164. New York: William Wood & Co., 1931. Price, $2.50.

THE asthma problem is presented from a European viewpoint, as yet not deeply influenced by the work of numerous American investigators in this field, especially from the standpoint of hypersensitiveness. Of 46 references in the book there are only 4 to the extensive American literature. While the many therapeutic measures which have been employed in the treatment of this disease receive the author's attention, there are numerous statements which must be challenged: "It is, of course, impossible to test out all the possible allergens separately." In suggesting tests with groups of related allergens, he says: "One group may consist of dust, fur, feathers and orris-root extracts." The statement that "In the case of children it is seldom practicable to perform skin tests because of the fear induced by scalpel or hypodermic needles" is certainly not in keeping with the experience of American allergists. Nor is his quotation of Moos that "Skin reactions to proven allergens fail to appear after adequate psychotherapy." Nor this: "Permanent residence at high altitudes can be relied upon to abolish the paroxysms in nearly every case." While he recommends the treatment of pollen-sensitive patients with pollen extracts, he deplores the length of time and expense involved: a proper objection to his own method in which he gives prophylactic injections every other day beginning early in December. The practitioner will find sounder advice in any one of a number of current American texts.

R. K.

THE INBORN FACTORS IN DISEASE. By A. E. GARROD, K.S.M.G., D.M., LL.D., F.R.C.P., F.R.S., Consulting Physician to St. Bartholomew's Hospital; sometime Regius Professor of Medicine in the University of Oxford. Pp. 160. New York: Oxford University Press, 1931. Price, $2.75.

THE older doctrines of diathesis, dealing with the morbid predispositions of the individual, were largely lost sight of with the rise of bacteriology in the latter third of the last century. More recently the concept "diathesis" is having a glorified rebirth in the doctrine of "constitution," which is being more and more taken into consideration in our study of disease. To quote: "The further nosology is pursued, the more clearly does it emerge that in every case of every malady there are two sets of factors at work in the formation of the morbid picture, namely internal or constitutional factors inherent in the sufferer and usually inherited from his forebears and external ones which fire the train." The author has

developed his theme in a manner that will be found interesting and convincing by the practitioner of medicine, who "wittingly or unwittingly, is constantly engaged in the study of constitutions and predispositions and of reactions to environment."

R. K.

CUTANEOUS *X*-RAY AND RADIUM THERAPY. By H. H. HAZEN, A.M., M.D., Professor of Dermatology, Medical Department of Georgetown University. Pp. 166; 28 illustrations. St. Louis: C. V. Mosby Company, 1931. Price, $3.00.

CLEAR, concise statements afford the keynote of this little volume on the therapeutic use of Roentgen ray and radium in dermatology. The material is based upon the author's personal experience with abundant reference to the work of other well-known dermatologists and roentgenologists.

In the first half the principles of irradiation therapy, equipment, technique and the action of radioactive substances are discussed. Of particular merit is the author's emphasis of the vigilance required in protecting the patient and operator against the harmful effects of irradiation.

The rest of the volume deals briefly with the character and amount of irradiation required in specific dermatologic conditions. Here the results obtained by the author and others must prove of inestimable value to workers in this field.

A fair knowledge of Roentgen ray and radium therapy, and of dermatology, is necessary to fully appreciate this book. As a handy reference for the busy radiotherapist this little volume will find its greatest value.

K. K.

BREAST FEEDING. By MARGARET EMSLIE, M.B., CH.B., late Senior Medical Officer for Maternity and Child Welfare, County Borough of Croydon. Pp. 142; 6 illustrations. New York: Oxford University Press, 1931. Price, $2.00.

THIS is the only book on this subject written by a woman that the Reviewer can recall. Convinced that the preparation for lactation is largely neglected, she devotes a large section to matters such as a high vitamin diet, development and support of the breasts and methods of everting, elongating and hardening the nipples. The management of breast feeding, its proper inauguration and means of increasing and prolonging the secretion of milk are fully considered. The characteristics of the normal breast-fed infant are explained and contrasted with those of the infant experiencing hunger, overfeeding, colic, vomiting and other difficulties of lactation.

The Reviewer has not found that infants do well on such a small

number of feedings as the author advises, nor does he agree with her that all colic is caused by air swallowing.

This book is in handy form, well arranged, well indexed and provided with a generous list of references. It can be endorsed as a thoroughly convenient and valuable exposition of this important subject, by one qualified for its authorship by a wide experience.

J. S.

BOOKS RECEIVED.

NEW BOOKS.

A Diabetic's Own Cook Book. By STELLA H. LYONS, with a Foreword by LOGAN CLENDENING. Pp. 94. New York: Alfred A. Knopf, 1932. Price, $2.00.

Cancer. What Everyone Should Know About It. By JAMES A. TOBEY, DR.P.H., with Introductions by JOSEPH COLT BLOODGOOD, M.D., and H. L. MENCKEN. Pp. 323; 17 illustrations. New York: Alfred A. Knopf, 1932. Price, $3.00.

La Maladie de Boeck. By A. KISSMEYER, Medecin de l'Institut Finsen. Preface by DR. J. DARIER. Pp. 147; 67 illustrations. Copenhagen: Levin & Munksgaard, 1932.

A Text-book of Medicine for Nurses. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., M.R.C.P., Senior Assistant Physician and Cardiologist, Royal Southern Hospital, Liverpool, etc. With a Foreword by MISS E. M. MUSSON, C.B.E., R.R.C., Chairman, General Nursing Council for England and Wales. Pp. 439; 38 illustrations. New York: Oxford University Press, 1931.

Publication on the Costs of Medical Care: No. 10. The Frontier Nursing Service. By ANNE WINSLOW, Executive Secretary, New York Office, Frontier Nursing Service. Pp. 16. Washington, D. C.: The Committee on the Costs of Medical Care, 1931.

Tumors of Bone. By CHARLES F. GESCHICKTER, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore, and MURRAY M. COPELAND, M.D., Memorial Hospital, New York City. With Forewords by DEAN LEWIS, M.D., and JOSEPH COLT BLOODGOOD, M.D. Pp. 709; 406 illustrations. New York: The American Journal of Cancer, 1931. Price, $5.00.

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Herz und Angst. By PROF. DR. LUDWIG BRAUN. Pp. 119. Wien: Franz Deuticke, 1932. Price, M 6.

The Fundus of the Human Eye. By ERNEST CLARKE, C.V.O., M.D., F.R.C.S., Consulting Surgeon to the Central London Ophthalmic Hospital, etc. Preface and Table of Contents with 51 colored plates. New York: Oxford University Press, 1931.

Prohibiting Minds. By STEWART PATON, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Pp. 198. New York: Paul B. Hoeber, Inc. Price, $2.00.

A Hand-book of Ocular Therapeutics. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S. Professor of Ophthalmology, Northwestern University Medical School, Chicago, etc. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $3.25.

Clinical Roentgen Pathology of Thoracic Lesions. By WILLIAM H. MEYER, M.D., Professor of Roentgenology in the New York Post-Graduate Medical School of Columbia University, etc. Pp. 272; 183 engravings. Philadelphia: Lea & Febiger, 1932. Price, $6.00.

Traitement de la Tuberculose par la Sanocrysine. By KNUD SECHER, Medecin-Chef à l'Hospital de Bispebjerg, Copenhague. Pp. 110; 21 illustrations. Copenhagen: Levin & Munksgaard, 1932.

Leonardo da Vinci. By PROF. DR. SIGMUND FREUD, LL.D. (University of Vienna). Translated by A. A. BRILL, PH.B., M.D., Lecturer in Psychoanalysis and the Psychosexual Sciences, Columbia University. Pp. 130; illustrated. New York: Dodd, Mead & Co., 1932. Price, $3.00.

Surgery of the Chest. By GEORGE F. STRAUB, M.D., F.A.C.S. Pp. 475; 341 illustrations, including 68 color plates. Springfield, Ill.: Charles C Thomas, 1932. Price, $10.50.

Spontaneous Pneumothorax in the Apparently Healthy. By HANS KJAERGAARD. Pp. 251; 29 illustrations. Copenhagen: Levin & Munksgaard, 1932.

NEW EDITIONS.

Recent Advances in Bacteriology. By J. HENRY DIBLE, M.B. (GLAS.), F.R.C.P., Professor of Pathology in the University of Liverpool. Pp. 476; 29 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, $3.50.

United States Army X-Ray Manual. Rewritten and edited by LT.-COL. H. C. PILLSBURY, M.C., U. S. A. Pp. 482; 228 illustrations. Second edition. New York: Paul B. Hoeber, Inc., 1932. Price, $5.00.

The second edition of this book includes the improvements in apparatus and technic which have been made since the previous publication. The portion devoted to interpretation is well presented.

Medical Dictionary. II Part, German-English. VI Edition. By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. Pp. 238. Wien: Franz Deuticke, 1932. Price, M. 7.—.

Applied Physiology. By SAMSON WRIGHT, M.D., M.R.C.P., Professor of Physiology, University of London, Middlesex Hospital Medical School. Pp. 552; 128 illustrations. Fourth edition. New York: Oxford University Press, 1931. Price, $5.50.

Manual of Surgery. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. *Vol. II. Extremities—Head—Neck.* Pp. 685; 303 illustrations. Eighth edition. *Vol. III. Thorax—Abdomen.* Pp. 578; 177 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, $3.80 each volume.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Elimination of Phenolsulphonphthalein by the Kidney.—The Influence of Pathologic Changes in the Liver.—HANNER and WHIPPLE write (*Arch. Int. Med.*, 1931, **48**, 598) that many years ago the latter noted that in certain cases of intoxication of pregnancy there was a high degree of elimination of phenolsulphonphthalein by the kidney and suggested that the explanation lay in liver injury. Subsequently it was observed that there was an unusual elimination of phthalein in experimental chloroform poisoning of dogs. These two observations naturally connote hepatic injury modifying the elimination of phthalein. Additional evidence has been brought forth by writers in the more or less recent past to show that the liver can excrete phthalein, the most definite information probably being that of Marsh and Vickers, who recovered 16 per cent of phthalein from the liver of dogs which were killed 15 minutes after the injection of 180 mg. of the dye. The work of Möller and Lundsgaard, furthermore, confirms the hypothesis that the normal liver plays a part in the elimination of phthalein; their work also shows that the dye is observed in the gastro-intestinal tract only in very small quantities. In order to investigate by experimental methods the question of the elimination of phthalein, the two authors poisoned a series of dogs with chloroform by light surgical anesthesia. They also attempted to injure the liver by administration of phosphorus. Injury to the liver was shown by a study of the blood fibrin and the icterus index, as well as by the elimination of phthalein. The second part of the experiment was performed by inserting a cannula into the common duct and collecting the bile and urine for 2-hour periods of time. The flow of phthalein in the bile could not be demonstrated. Control experiments were performed under ether anesthesia and by obstruction of the bile ducts. Elimination of the dye by way of the gastrointestinal tract was determined by feeding 30 mg. of phthalein through the stomach tube to the dog. Only 3 to 5 per cent appeared

in the urine and only traces in the feces, demonstrating the absence of intestinal absorption in the reactions that were studied by the authors. It may be deduced from these experiments, taken *in toto*, that the liver of the normal dog is capable of eliminating through the bile 10 to 15 per cent of the usual dose of phthalein and the surplus, when this way of escape is blocked, appears in the urine, giving very high figures. Not more than 5 per cent of the amount of phthalein that is excreted into the duodenum is reabsorbed. In the dog that has necrosis of the liver produced by chloroform poisoning from 90 to 97 per cent of the dye is eliminated through the kidney as contrasted with the control of from 75 to 78 per cent. The normal figures return when the hepatic injury is repaired. These experiments are of considerable practical value. From time to time excessive elimination of the dye is noted by the clinician who is wont to ascribe this abnormality to some fault of the technic. Hanner and Whipple now show that the explanation lies in pathologic changes in the liver. It is obvious that renal and hepatic disease when combined will disorganize the phthalein test for kidney efficiency. It is likewise obvious that high phthalein elimination indicates liver injury and that the phthalein test may be used as a functional test for liver disease as frequently as it is for kidney disease except that the results from the one are exactly the opposite to the other: high urinary output when there is liver disease; low when there is kidney disease.

SURGERY

UNDER THE CHARGE OF
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Acquired Renal Dystopia or Movable Kidney.—KIDD (*J. Urol.*, 1931, **26**, 327) reviews the types of renal dystopia. A fresh hypothesis is formulated which attributes the most important pathologic type to the persistence from neolithic times of a racial stock of Egyptian origin and descent. The importance of the intraäbdominal pressure is minimized and the importance of the suspensory ligaments of the kidney are emphasized. The pathology of movable kidney is placed on a fresh plane and is brought into line with the pathology of sprains and deformities. Pyelography is advocated as the only real guide to treatment and as the indicator of the reasons for success and failure of operations. An operation for renal dystopia is described and the points essential for success in operating outlined.

Tumors of the Kidney.—SMITH and FERRIS (*Am. J. Surg.*, 1931, **13**, 552) state that they are inclined to feel that these tumors all have a common origin, probably from some prenephric rest, and that the differences are inherently due to the particular reaction of the individual rather than to any fundamental differences in the cells of origin. It is not important clinically to know whether a tumor arises from displaced celomic lining cells or from nephridial rests, except as its clinical behavior varies. In these tumors no inherent differences are apparent in their clinical course, except in degree. Tumors of presum-

able adrenal origin are apt to be slower growing, but may metastasize by the blood stream very early. They perhaps represent slightly more differentiated epithelium than do the tumors of renal origin, but their fundamental cell prototypes are essentially the same, which brings the author to the conclusion that Wilson reached 20 years ago of the underlying mesothelial origin of the entire group. Finally, in reviewing the embryonal tumors of infancy and childhood, the current theory of renal blastoma origin has been accepted. The writers feel that the evidence is sufficient to show that these cells are capable of differentiation even into the bizarre and curious, almost teratoid tumors which we occasionally find. It is but a step from accepting the conception of the origin of embryonal tumors to recognizing that the adult hypernephroma may well arise merely from a later stage of differentiation of the renal blastoma.

The Separate Neural Arch.—Willis (*Bone and Joint J.*, 1931, **13**, 709) says that the series of 1520 human skeletons at his disposal discloses separate neural arch made by the pedicles, laminæ and spinous processes posteriorly in 79, or more than 5 per cent. In vertebral columns with 25 presacrals the incidence is almost twice as great as in columns with the regular 24, but the actual percentage is an accident of the sampling, rather than a criterion of the population at large. Study of the defect, whether unilateral or bilateral, substantiates its essential origin in a skeletal anomaly, and assigns a very minor rôle to trauma. Embryologically the defect falls into the category of anomalous ossifications, of which there are many other examples scattered over the skeleton. It is an anomaly peculiar to the lumbar region and may be found in any lumbar vertebra and on either or both sides, but is usually confined to the last presacral. Thus spondylolisthesis may be a sign of the anomaly. Trauma plays a secondary rôle in this condition, finding the fibrous tissue a point of less resistance to strain than some structure. Separate neural arch in its origin resembles spina bifida, defective articular processes and separate bony centers for transverse mammillary and accessory processes which are peculiarly associated with the lumbar column. It is found more frequently when some other anomaly, such as the twenty-fifth presacral, is present. It is the ultimate result of imperfect ossification whether this be caused by failure in the ossific process itself or by a defect of the preëxisting cartilage.

Split Heel Approach in Osteomyelitis of Os Calcis.—Goenslev (*J. Bone and Joint Surg.*, 1931, **13**, 759) says that a series of 11 cases of osteomyelitis of the os calcis, 9 pyogenic and 2 tuberculous, have been presented because radical treatment by the split heel or cloven heel method has been eminently satisfactory, there having been no persisting sinuses and but one recurrence to date, the latter occurring in 1 of the cases of tuberculosis. Periosteal stripping and removal of healthy cortical bone is avoided. A minimum of healthy cancellous bone is sacrificed and tunneling is avoided. Sinuses should be disregarded in the incision as they invariably close, providing all dead bone is removed. The plantar scar is so deeply situated that the plantar tissues form two thick cushions well adapted to weight bearing without pain.

THERAPEUTICS

UNDER THE CHARGE OF

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The Influence of Digitalis Bodies on the Pulmonary Bloodflow.—Employing a somewhat modified histamin method, whereby a new cholin derivative was used, PRUSIK (*Ztschr. f. Krebsforsch.*, 1931, **23**, 513) presents the results of a series of investigations on the influence of strophanthin or digitoxin on the speed of pulmonary circulation. He finds that where the pulmonary circulation is normal the digitalis bodies exercise little effect. Where it is more rapid than normal, as in uncomplicated Graves' disease, there is a marked tendency for the pulmonary circulation to be slowed both immediately and at the end of 24 hours. On the other hand, in patients with cardiac failure whose pulmonary circulation is slower than normal, the digitalis bodies show a marked tendency to accelerate this circulation, returning it to normal or even temporarily to a rate greater than normal. He compares his results with those reported by Weiss and Blumgart, and calls attention to the fact that his observations were made at shorter intervals of time after single large doses of the drugs, which may account for his more consistent results. He summarizes his findings by saying that the tendency of digitalis bodies is toward a restoration of pulmonary circulation in the direction of normal. That is, its delay where it is overfast and its acceleration where it is too slow.

The Vital Hormone of the Adrenal Cortex.—HARTMAN, BOWEN, THORN and GREENE (*Ann. Int. Med.*, 1931, **5**, 539) presents a report upon the actions of the adrenal extract, cortin, both upon experimental animals and upon man. Administration of cortin to adrenalectomized cats maintains them alive and healthy for an indefinite period during which they feel perfectly normal even to the extent of one female's going into heat and becoming pregnant. Its administration immediately after operation also permits the simultaneous removal of both adrenal glands with recovery. Adrenalectomized cats allowed to approach death can be made to recover completely with cortin. The administration of increasing quantities fails to produce signs of overdosage. Its administration to young adrenalectomized rats permits normal growths and development. Cortin also promotes the healing of wounds and raises the resistance of adrenalectomized animals to bacterial toxins. Finally, it raises to normal the resistance to cold which is so greatly reduced by adrenalectomy. In man with adrenal deficiency its adminis-

tration restores the normal contractile power of muscle and raises its resistance to fatigue when tested by the ergometer. One case of a young man with virtually complete loss of adrenal function due to Addison's disease is reported in which the administration of cortin restored health, vigor and nutrition approximately to normal. On withdrawing cortin relapses occurred each of which was controlled promptly by its readministration. After 224 days of maintenance of fair health the patient acquired acute bronchial pneumonia and died. Autopsy proved the presence of great destruction of the adrenals confirming the diagnosis of Addison's disease. A second patient with Addison's disease was observed but died before cortin could be administered in adequate doses. Administration of cortin to a patient with hypothyroidism caused marked restoration of muscular strength without change in basal metabolism or other beneficial effects except a moderate increase in blood pressure. A similar response was observed in the muscular strength of a patient with hyperthyroidism, some improvement was observed in the muscular functions in 2 cases of muscular atrophy and in 1 of muscular dystrophy. Finally, clinical improvement was produced in some cases of severe postinfectious asthenia.

PEDIATRICS

UNDER THE CHARGE OF

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The Hilus of the Lung in the Child.—ALTSCHUL (*Radiol.*, 1931, **17**, 1147) believes that the radiologic diagnosis of tuberculosis of the bronchial lymph nodes is not made as often as it should be, especially in children. The width of the hilus does not furnish important evidence for the diagnosis. The density of the hilus is more important than the width. A hilus showing increased density is always questionable, whether there is a general increase of density or of smaller circumscribed foci presenting increased density. In children calcification in the hilus is rare. Great importance should be attached to the comparison of the two hilus shadows. Inequality of the shadows is definite for the diagnosis. In making this comparison one must show both hili in their entire extent, which can be accomplished only by turning the patient about slightly on the body axis. In the majority of cases any enlargement of the lymph nodes is due to tuberculosis. In cases that are not just recent a primary focus of the lung as the starting point of the lymph gland involvement can usually be shown. If such a primary focus cannot be demonstrated it must be remembered that there are other infectious processes that may give rise to the enlarged lymph glands. Often long or short dense strands extend to the hilus, particularly from the lower field. These are due in part to infiltrated lymphatic tracts and in part to inflammatory changes in the connective tissue. Certain groups of lymph glands cannot be shown in the roentgenogram as they fall within the middle shadow. In the absence of positive roentgenographic observation, an involvement of the lymph glands cannot be excluded. The roentgenographic examination in itself

does not suffice for the establishment of the diagnosis and must be supplemented by other clinical methods of examination. The Roentgen ray examination constitutes the most important part of the examination, and without it an accurate diagnosis of hilus involvement is impossible.

Effect of Curd Tension on the Digestibility of Milk.—Espe and Dye (*Am. J. Dis. Child.*, 1932, **43**, 62) found that doubling the curd tension of milk increased the length of the digestive period from 30 to 65 per cent. A normal milk of high curd tension usually means a more concentrated milk than one of low curd tension, and, therefore, one of greater food value. The percentage of casein in the milk seems to be the greatest factor influencing curd tension. The disparagement between soluble proteins and curd tension is even greater. Boiling markedly lowers the curd tension of milk. Acidifying the milk before its coagulation with rennin has the opposite effect as it raises the curd tension. The addition of small amounts of various substances, such as calcium chlorid and sodium citrate, also has a marked effect on curd tension. Diluting milk with water has the same effect on curd tension as diluting it with its own whey. Dilution has a greater effect than merely producing a less concentrated mixture.

Bacillus Mucosus Infection of the Newborn.—Jampolis, Howell, Calvin and Leventhal (*Am. J. Dis. Child.*, 1932, **43**, 70) state that an outbreak of infectious diarrhea developed in a nursery for the newborn. Its spread was insidious, and a latent period of two months elapsed after the first few cases appeared. The constitutional symptoms, severe intoxication, dehydration and prostration were out of proportion to the relatively mild diarrheal symptoms. The stools averaged about 6 a day. They were watery and contained mucus but no blood or pus, except in 1 case. The mortality was high in spite of the usual accepted treatment for anhydremic intoxication. Apparently the offending organism was Bacillus mucosus, the virulence of which may have been increased by symbiosis with anhemolytic streptococci. Bacillus mucosus was isolated from the nasal secretions, stomach contents, stools and intestinal mucosa in a large number of cases. None of the usual organisms causing infectious diarrhea, such as the typhoid-dysentery group, were found. The primary and outstanding pathologic findings in the fatal cases consisted of acute enteritis. The mucous membrane was red, swollen, finely granular and covered with reddish-gray mucus. Microscopic examination showed the mucosa to be infiltrated with polymorphonuclear leukocytes and lymphocytes. A few shallow ulcers were found, and the lymphoid tissue was hypertrophied. There was a relative absence of involvement of the colon, which probably accounts for the comparatively few diarrheal stools and the absence of pus and blood. In only a few instances was there evidence of parenteral infection. In a few babies terminal bronchopneumonia and otitis media developed. Bacillus mucosus and anhemolytic streptococci were found in the discharges from the ears and from the lungs. The cultures from the throats of 3 nursery maids gave pure growths of Bacillus mucosus, and when these 3 individuals were relieved from duty in the ward the outbreak promptly subsided, and there were no recurrent outbreaks.

DERMATOLOGY AND SYPHILIS

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Lupus Erythematosus Disseminatus.—MOOK, WEISS and BROMBERG (*Arch. Derm. and Syph.*, 1931, **24**, 786) present in detail the case histories of 13 patients with disseminated erythematous lupus and while disclosing no new facts their material is a valuable clinical study of 9 fatal cases, 4 of which came to autopsy. In 6 of the fatal cases the duration of the disease was less than 1 year. Remissions were a feature of most of the cases. Leukopenia as an important diagnostic sign and the polymorphism of the cutaneous picture are again stressed. Involvement of the serous cavities was conspicuous in the material studied. The authors feel that insufficient evidence is still at hand to subscribe to the tuberculous etiology so often proposed for this striking and tragic dermatosis.

A Short Review of Alopecia of the Scalp.—PHOTINOS (*Acta Derm.*, 1931, **18**, 22) gives the differential diagnosis involved in the clinical evaluation of the scalp alopecias with special reference to the pseudopelade of Brocq, a subject upon which the author has already written a large monograph. Pseudopelade is a type of cicatricial alopecia occurring for the most part in male adults and characterized by small bald patches which have a predilection either for the occiput or the vertex and midportion of the scalp. The number of lesions is in inverse ratio to their size, the smaller the patches the greater the number. Although the patches are irregular in contour they are strictly limited at the borders, which frequently jut out into surrounding parts of the scalp in quite a different fashion from the round and oval lesions of alopecia areata. The hair which may remain within the patches or at the borders is usually normal in appearance although some of it can be easily pulled out, showing a succulent, whitish, glassy sheath. The skin of the patches is white, smooth and atrophic, and slightly but definitely depressed below the level of the surrounding skin. There is a complete absence of inflammatory signs so conspicuous in folliculitis decalvans, a type of cicatricial alopecia resembling pseudopelade except for the presence of follicular pustulation during the active stage. The etiology of pseudopelade is undetermined, the prognosis *nil* for restoration of hair and uncertain for arrest; the treatment, the local use of either sulphur or mercury.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Radium Therapy of Menarchial Hemorrhage.—That type of excessive menstruation which occurs in adolescent girls and which is often termed menarchial hemorrhage has often been a cause of great concern to the gynecologist because in girls of this age conservatism must be the rule except in extreme cases. KELLY (*J. Am. Med. Assn.*, 1931, **97**, 760), who was one of the pioneers in the use of radium irradiation in gynecology, presents the results in a series of 30 patients ranging in age from 13 to 25 years who were treated with radium for this condition. In each patient the health was impaired and there was a varying degree of secondary anemia. In 6, the hemoglobin was between 30 and 60 per cent. There were 16 cases in which the period became normal immediately or soon after the treatment and remained so. In 5 there was a temporary amenorrhea with a later return or normal menstruation. There was a group of permanent amenorrhea consisting of 6 cases although in 4 of them sufficient time has not elapsed to be sure of a permanent cessation. He is of the opinion that radium and Roentgen rays find their most brilliant field in the treatment of menopausal hemorrhages, to which most gynecologists subscribe. In the type of cases under discussion, irradiation is also of great value as it usually spares the patient a surgical operation of a radical nature. It is important however, to begin the treatment with the small broken dosage plan and work up through two or three treatments to the efficient amount; in other words, more treatment can always be given when necessary but once an overdose has been given a lasting amenorrhea may be the result. In this series the smallest amount of radiation given was 184 millicurie hours and the largest, 925, the average dose being 583.

Carcinoma of the Ovary.—As a result of a study of a series of cases of cancer of the ovary which were admitted to the gynecological service of Stanford University, EMGE (*California and West. Med.*, 1931, **35**, 366) has reached the conclusion that this disease whether primary or secondary, offers a gloomy outlook because of the absence of early symptoms. Menstruation, if still present, may not be much influenced. Pain appears very late and only when the tumor mass has grown to a considerable size or has encroached upon other structures in the pelvis. About half of the patients were disturbed by urinary frequency, dysuria or retention, while loss of weight and ascites are also common symptoms. All of the patients had easily palpable masses while cachexia and secondary anemia, corresponding in degree to the

size of the mass and the metastatic involvement, were noticed in about 60 per cent of the patients. Radical surgery is usually indicated and may be advantageously combined with irradiation with the prospect of prolonging life for a period of 5 years with occasional cures. He has noted no instance in which the removal of a primary ovarian cancer caused the disappearance of metastatic tumors elsewhere. As a matter of prophylaxis, he believes that all newgrowths of the ovary should be removed as soon as discovered regardless of the age of the patient since the percentage of malignant degeneration is high, being 22.8 per cent in this series.

OPHTHALMOLOGY

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The Pathology of Papilledema.—The theories in regard to the pathology of papilledema may be divided into the mechanical and the non-mechanical. The mechanical types may have to do either with a disturbance of the lymph flow or with an interruption of the vascular supply of the optic nerve. The non-mechanical types may be either inflammatory or toxic. Since the discovery by Schwalbe, in 1869, of a connection between the subarachnoid space of the brain and that of the optic nerve, theories of the mechanical origin of papilledema have been supported by experimental work of Schmidt-Rimpler, Manz, Cushing and Bordly, and Schieck. Schmidt-Rimpler believed that there was a direct driving forward of the cerebrospinal fluid through the lamina cribrosa, with an edematous infiltration of the nerve head as a direct result, while the explanation of Manz was based upon compression of the central vessels of the retina as they passed through the lamina cribrosa. Cushing and Bordly corroborated this work. A different type of explanation was advanced by Schieck who believed the condition was caused by the entrance of the cerebrospinal fluid under increased pressure in the preformed perivascular lymph spaces of the axial bundle of the optic nerve and along the central vessels into the disk. The position of the central vein in the optic nerve determines the amount of compression of the perivascular lymph spaces and has been studied by several investigators. Fry (*Am. J. Ophthal.*, 1931, **14**, 874) examined a series of 40 eyes obtained from 21 cases. In 17 of the cases the diagnosis was brain tumor, in 2 of the cases meningitis and there was 1 case of brain abscess, 1 of gumma of the brain and 1 aneurysm. In 32 of the eyes examined there was a papilledema present and all but 2 of them the condition was recent. The average swelling was $3\frac{1}{2}$ diopters. The course of the central artery and vein as they leave the nerve was studied to determine where

pressure occurred along the course of the vessel that could result in the edema of the nerve head and nerve fiber layer of the retina. This compression was found to occur in the subarachnoid space in 62 per cent and in the side of the nerve in 38 per cent of 26 eyes showing papilledema. Compression of the nerve was found in 84 per cent of 31 eyes showing papilledema. The evidence was in favor of active compression of the central vein by an increased fluid pressure within the nerve pressing forward into the eye. Fry believes that the edema of the nerve head which produced the characteristic ophthalmoscopic appearance of choked disk occurs also in the subpial portion about the central vessels in the nerve stem. The diameters of the nerves, anterior and posterior to the entrance of the central vessels, were the same in 6 cases, and in 1 the diameter posterior was greater. In the remaining 17 instances the anterior diameter was greater, showing the greater amount of edema anteriorly. Evidence of inflammatory change as a cause for papilledema could not be found. The initial cause of papilledema is a compression of the central vein of the retina along the side of the nerve or in the subarachnoid space. This produces a venous stasis with a consequent transudation of lymph into the tissue of the optic disk and adjacent nerve fiber layer of the retina. The secondary cause is a forward pressure of fluid within the optic nerve, produced in all probability by the infiltration of cerebrospinal fluid under increased pressure in the perivascular lymphatic spaces.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Noises of Civilization and Their Evil Effects.—Largely by utilization of tools has man become differentiated from other animals. It was inevitable in this "age or machinery" that noise should increase. WELLS (*Ann. Otol., Rhinol. and Laryngol.*, 1931, **40**, 143) roughly classifies the world's noises as originating from such causes as: animate nature; war; building and construction; traffic and transportation; manufacture; commerce, and communication. After discussing the various types of noises, qualitatively and quantitatively, the author states that the deleterious effects of noise may fall chiefly on the auditory apparatus, *per se* or on the general nervous system. The hearing organ may be affected: (1) By loss of function; (2) by developing abnormal sensitivity, or (3) acquiring a tolerance, to the noise.

It is a fundamental physiologic law that an organ exposed to excessive stimuli must either adapt itself thereto or suffer harm. Phylogenetically, as the youngest of our special senses, audition is frailer than any of the others. Noise deafness is not unduly common and ordinarily results from long continued contact with high-pitched, intense, disagreeable and annoying noises—as in the well-known boiler-maker's deafness. The impaired hearing of aviators is due to

noise and often also to tympanic lesions from other obvious causes. Railroad engineers, miners, "sand hogs," riggers, etc. also get "nerve deafness," which however is due more to concussion than to noise. Following a philosophic discussion Wells, concludes ". . . . or will not science find some effectual means to rid us of this unwholesome by-product, so that civilization may eventually reach the goal which is its aim?" (rest and quiet).

Concussion Deafness of Miners With a Survey of the Motor Apparatus in Modern Mines.—For the purposes of his presentation, KATZCHINANN (*Ztschr. f. Laryngol., Rhinol.*, 1931, **20**, 353) distinguishes between deafness due to noise and due to vibration (concussion). Moreover, "concussion" is employed in the sense of continuous, multiple, corporeal vibrations rather than a sudden explosion (usually causing rupture of the ear drum) or a cranial injury with concussio cerebri or tympanic and labyrinthian trauma.

This vibration or concussion deafness, as interpreted by the author, occurs oftenest in workers subjected over a long period of time to incessant and rapid vibrations, with or without excessive noises—notably in railroad engineers, miners, riveters, riggers, etc. In miners the condition appears to have arisen since the introduction of compressed-air or motor-driven machinery. The lesion is essentially one of the auditory perceptive apparatus. An attendant "rushing, hissing or humming" tinnitus makes the miner "irritable, apprehensive, and suspicious." Both the deafness and the tinnitus increase the underground miner's liability to accident; and is obviously, therefore, of medicolegal importance. Vertigo is absent, the vestibular organs apparently escaping. Like any other occupational disability, the treatment is prevention. The technicalities of mining machinery is discussed.

RADIOLOGY

UNDER THE CHARGE OF

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Roentgen Treatment of Chronic Leukemia.—MCALPIN, GOLDEN and EDSAL (*Am. J. Roent. and Rad. Therap.*, 931, **26**, 47) relate their experience with Roentgen treatment in 24 cases of myeloid leukemia and 23 of lymphatic leukemia. In the first group 18 patients died after an average illness of 3 years, and 5 are living but with a shorter average illness. In the second group 16 patients died after an average illness of 1 year 6 months, and 5 are living with an average of 4 years 6 months. These writers maintain that every patient is more or less an individual problem. A blood count should be made before each treatment. Small doses of Roentgen rays to the enlarged nodes and spleen in the

lymphatic type, one area at a time, and to the spleen in the myelogenous type, are advised. The patient should be treated regularly, at first every week; later the period may be lengthened when the response and susceptibilities of the patient have been established.

Criteria of Acute Intestinal Obstruction; Value of Roentgen Ray Evidence.—Intermittent, crampy, colicky pain, associated with nausea and vomiting but unattended by local physical findings, suggests acute intestinal obstruction, says WANGENSTEEN (*Radiology*, 1931, **17**, 44). Shadows of gas in the small intestine demonstrate the presence of intestinal stasis. The "ladder pattern" of gas distention in the small bowel need not be awaited to make the diagnosis. In simple obstruction gas can usually be visualized in the small bowel within 4 or 5 hours after the onset of symptoms. When the obstruction is due to strangulation the gas does not appear as early as in simple obstruction. In the inhibitive ileus of peritonitis, gas distention of the small bowel may be observed early. Distention of both colon and small intestine is almost invariably present. Dense "bands" between the intestinal loops are indicative of exudate between the intestinal coils.

Osseous Changes in Hyperparathyroidism. — Roentgenographic changes observed in the osseous system in 2 cases of hyperparathyroidism associated with tumor of the parathyroid gland are described by CAMP and OCHSNER (*Radiol.*, 1931, **17**, 63). The roentgenographic changes comprise generalized osteoporosis, cystic lesions and deformities. The generalized osteoporosis is characterized by a miliary or granular appearance, is best observed in the skull, and seems to be peculiar to hyperparathyroidism. In addition, the trabeculæ and cortical bone are thinned, and areas of subperiosteal absorption are seen in the long bones and phalanges. Single or multiple cystic lesions are found in the jaw, pelvis and long bones, and are often confounded with those of osteitis fibrosa and giant-cell tumor. The deformities caused by softening of the bones consist of kyphosis, narrowing of the pelvis, coxa vara, bowing of the legs, and infractions. Renal calculi are not uncommon. In each of the 2 cases removal of the parathyroid tumor was followed by definite arrest of decalcification and progress toward restoration of the normal bone structures.

Physical Therapy Measures in the Treatment of Burns.—In the treatment of extensive infected burns, PECK (*Arch. Phys. Therap., X-ray, Rad.*, 1931, **12**, 327) has found heat and ultraviolet radiation to be valuable aids to skin-grafting. The heat, applied after grafting, was derived from an "oven baker," and a temperature of 100° F. was maintained about the injured parts, which were kept covered by moist dressings. Ultraviolet radiation was used in preparing the wound surfaces for grafting. It appeared to decrease the amount of surface infection and to promote more rapid formation of healthy granulation tissue. When the infection was marked, an initial exposure of 100 to 150 per cent of the erythema dose was given, and this was followed by smaller doses. After about 2 weeks the wound was ready for skin-grafting, and the heat treatment was then also supplemented by renewed ultraviolet radiation.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Stuttering.—BLANTON (*Ment. Hyg.*, 1931, **15**, 2, 270), states that speech is the index of the mind; not only the index, but the very medium through which the mind is formed and developed. No child should leave school with a defect of speech if it is possible to remedy it. Stuttering, especially, should receive the attention of teachers everywhere, for it not only causes a blocking or hesitations in the outward speech, but disturbs the emotions so that clear thinking is often impossible. It may show itself as a complete blocking of the speech or a repetition of initial sounds is any imaginable combination of these two symptoms. There is no dividing line between the frank stutterer who shows blocking and hesitation, and the person who is nervous, embarrassed, and timid when called upon for speech. Speech is a medium of group social adjustment. Stuttering is a symptom of an inability to adjust to the group. It is caused by a fear, a timidity, or a negative (hate) attitude toward the group. To understand the cause of stuttering in an individual, it is necessary to study first, the development of the emotional life of the stutterer and second, the nervous and muscular system of this person. Psychoanalysis alone, is not an effective method of treating stutterers. Speech training must also be used in most of these cases to get adequate results. The physical symptoms of stuttering are explained by the fact that speech is made up of muscle movements that have a more primitive function. Breathing movements, chewing movements, suckling movements, coughing, and vomiting movements, are all coördinated through the speech area into the unified movements of speech. When there is an emotional blocking of the control of the higher brain centers over these lower brain centers, each lower brain center tends to act independently, but it is the early fixations that determine whether the stuttering shall consist of a repetition of sounds, or a vomit-like blocking, or a suckling movement. The psychologic causes that lie back of stuttering—the fixation of the libido at the oral, or anal-erotic stage and at the narcisistic stage, make the stutterer so sensitive to the attitude of others that he is often unable to speak normally. Other causes of stuttering are left-handedness, and developmental defect of organic, constitutional or functional nature in the muscular and nervous system underlying speech. The treatment of stuttering comprises physical hygiene, mental hygiene, and speech training—each of which the author discusses quite adequately and in a well-rounded manner.

On the Treatment of Tabetic Optic Nerve Atrophies With Sulphur.—WINKLER (*J. Nerv. and Ment. Dis.*, 1931, **73**, 276) declares that optic nerve atrophy of tabes is characterized by: (1) Disappearance of the most tender septal ramifications and of their bloodvessels, then a club-shaped thickening of the bigger septa; (2) the glia fiber system, mediating for the nourishment of the nerve fibers from the bloodvessels, first shows a spotty sclerotic thickening and will disappear later; (3) the sheaths of the nerve fibers tumefy at the center, later are destroyed and secondarily destroy the axon itself. In the pathogenesis of the optic atrophy the nutritive trouble caused by the destruction of the glia and the capillaries must play the leading rôle. To this is added a toxic action. Assuming this to be correct, then only such a therapy can be successful, which beside improving the blood and lymph circulation of the optic nerve, will also promote the elimination of the spirochetal toxin by neutralization or by a rapid transportation from the organism, and will raise the resistance of the nervous glial elements against these toxins, vivifying the intermediary metabolism and also the elimination of the local toxin. This therapy is adequately supplied by intramuscular injections of sulphur. After treatment the changes noticed are: (1) Improvement of visual acuity; (2) enlargement of the visual field; (3) reappearing of color vision, and (4) changes of the grayish discoloration into red, due to improved circulation. The observed result has proved permanent to the present time.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Pulmonary Asbestosis in a Dog.—SCHUSTER (*J. Path. and Bact.*, 1931, **34**, 751) reports the autopsy findings on a dog which had lived 10 years in an asbestos factory. The animal had had dyspnea for the last 2 years of its life, lost considerable weight, and was finally killed as it became helpless. The lungs were small and showed a diffuse shotty induration. The pleura was markedly thickened. There was no evidence of pneumonia, hemorrhage or tuberculosis. The author regards the lung changes as an uncomplicated picture of asbestosis, characterized by an interstitial fibrosis, dilatation of bronchioles and the presence of numerous asbestos spicules. "Asbestos bodies" (described by COOKE, *Brit. Med. J.*, 1927, **2**, 1024) were lacking in the lungs of this dog. The author regards these bizarre formations as the product of infection superimposed upon asbestosis.

The Anticarcinogenic Action of Dichlorodiethylsulphid (Mustard Gas).—BERENBLUM (*J. Path. and Bact.*, 1931, **34**, 731) reports the results of further experiments along the same lines as his earlier work on mice showing that mustard gas inhibits the tumor producing properties of tar, from which the author concludes that mustard gas exerts a purely local action upon the mouse skin causing it to become refractory to the carcinogenic action of tar. This refractory state develops almost as soon as the mustard gas treatment is begun and subsides very soon after this treatment is discontinued. No distinctive histologic changes could be attributed to the mustard gas, a fact which inclines the author to abandon his earlier view that the tumor inhibition was due to a "superoptimal degree of irritation." He now suggests that mustard gas may exert some specific chemical action on the tissues rendering them refractory to the carcinogenic properties of tar.

Flocculation Reaction With Staphylococcal Toxin.—BURNET (*J. Path. and Bact.*, 1931, **34**, 759) studied the flocculation phenomenon that occurs when staphylococcal toxin and antitoxin are mixed under certain conditions. The author found that this reaction in many respects was similar to that obtained with diphtheria toxin. Flocculation actually represented a precipitation of the product of toxin-antitoxin union for, by suitable methods, either toxin or antitoxin could be liberated from the washed floccules. The point of optimal flocculation was found to be constantly related to the tube in the mixtures that contained equal quantities of toxin and antitoxin but it always occurred in the zone, from this neutral point, of excess antitoxin. The point of optimal flocculation did not indicate a "natural" equivalence of toxin and antitoxin. The flocculation of toxins modified by formalin treatment and by heat was also described and compared with the other properties of such preparations.

Blood Cultures in Chronic Infectious Arthritis.—BERNHARDT and HENCH (*J. Inf. Dis.*, 1931, **49**, 489) endeavored to confirm the finding of CECIL, NICHOLLS and STAINSBY (*Am. J. Med. Sci.*, 1931, **181**, 12) that streptococci could be isolated from the blood stream of patients suffering from chronic infectious arthritis in 62.3 per cent of cases. A survey of previous bacteriologic studies was made and 780 cases collected, microörganisms had been isolated in 26 per cent of these, with streptococci forming 18 per cent. Twenty patients in the active stage of rheumatoid arthritis afforded the material for the present investigation. Blood culture was carried out for 30 days by three different methods, including that published by Cecil, Nicholls and Stainsby. The media used by the latter writers had, however, been fractionally steam sterilized while that used by the authors was autoclaved. Contrary to the results quoted above, streptococci were not found in any of the cultures. Growths were obtained from 5 of the patients, 4 were staphylococci and the fifth a diphtheroid organism. The authors do not consider their results as an argument for or against the infectious theory of this type of arthritis, but point out that it is extremely difficult, with present cultural methods to isolate microörganisms from the blood of people suffering from the condition studied.

HYGIENE AND PUBLIC HEALTH

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An Epidemiologic Study of Typhoid Fever in Six Ohio River Cities.—VELDEE (*U. S. Pub. Health Rep.*, 1931, **46**, 1460) points out that the sanitary control of the public water supply is for the purpose of preventing water-borne diseases, especially typhoid fever, and the pollution of the raw water of the Ohio River is notorious. It is shown that prior to purification the typhoid rate was very high and that the disease occurred throughout the year. After purification of supplies was inaugurated the disease was much reduced and became one limited to summer and fall. In the opinion of the author it can no longer be attributed to water.

Cultivation of Vaccine Virus for Jennerian Prophylaxis in Man.—RIVERS in a previous communication has described a simple medium for the cultivation of vaccine virus. The results of the work reported at that time clearly indicate that vaccine virus is capable of multiplication in the presence of minced chick embryo tissue suspended in Tyrode's solution. The experiments, however, were conducted with a neurovaccine virus and, although the active agent engendered in cultures caused typical vaccinal lesions in rabbits, it was deemed best not to test it in human beings. To obtain a culture virus for Jennerian prophylaxis in man it seemed advisable to adapt a dermal strain of vaccine virus to the particular method of cultivation. The present paper (*J. Prev. Med.*, 1931, **54**, 453) deals with the results of this work. The medium employed for the *in vitro* cultivation of vaccine virus is exceedingly simple, but one must remember that it contains living cells. In spite of recent reports to the contrary, no one has definitely shown that vaccine virus is capable of pollution in the absence of surviving susceptible cells. Several kinds of media have been devised for the production of vaccine virus. The one described in this paper, however, is the best of the lot already proposed, because, inasmuch as neither serum nor plasma is used, and since the tissue consists of minced chick embryo, it is the least likely to become contaminated by an extraneous virus injurious to man. Furthermore, the virus produced in this manner remains potent in 50 per cent glycerol at +2.5° C. for at least a month. More information, however, concerning the length of time the culture vaccine remains active under a variety of conditions should be obtained, and to this end experiments are now being conducted. A dermal strain of vaccine virus has been adapted to a simple culture

medium consisting of minced chick embryo suspended in Tyrode's solution. The bacteria-free culture virus thus obtained produces in lower animals and in man typical vaccinia that renders them refractory to infection with ordinary vaccine virus harvested from calves.

The Effect of Irradiation With Ultraviolet Light on the Frequency of Attacks of Upper Respiratory Disease (Common Colds).—DOULL, HARDY, CLARK and HERMAN (*Am. J. Hyg.*, 1931, **13**, 460) report the results of studies of a group of adult volunteers, numbering 363, who were kept under observation from September 29, 1929, to May 31, 1930, a period of 35 weeks. A vigorous effort was made to secure reports of all cases of upper respiratory disease (common colds). From this number, approximately one-half was selected at random for irradiation, which was given over the first 31 weeks of the period. Mercury-vapor lamps were used and the intensity of erythema-producing rays was measured biweekly. The dosage was light to moderate, the individuals being stripped to the waist and exposed, either on chest or back on each occasion, to that dose, which from previous experience with the subject, seemed likely to produce only a minimal erythema. Total incidence for the period was slightly higher for the irradiated (receiving more than 10 treatments) than for the controls. Also cases of a more severe type, as evidenced by absence from duty and confinement to bed, by occurrence of fever, by productive cough or by long duration, were just as frequent in the irradiated as in the control group.

The Weil-Felix Reaction in Endemic Typhus Fever and in Rocky Mountain Spotted Fever.—SPENCER and MAXCY (*U. S. Pub. Health Rep.*, 1930, **45**, 440) refer to the fact that the Weil-Felix reaction has been regarded as highly specific of typhus. After a description of the cultures and technique they state the following conclusion: The Weil-Felix reaction is positive in a large proportion of cases of Rocky Mountain spotted fever. The mechanism of this reaction, although similar, is not exactly identical with that occurring in typhus fever. There is a qualitative difference.

PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF FEBRUARY 23, 1932

Evidence for the Existence of Amino Groups on the Serum-sensitized Surface.—ELEANORE W. JOFFE and STUART MUDD (from the Department of Bacteriology and the Henry Phipps Institute, University of Pennsylvania). The combination of antigen and antibody is dependent upon the specific chemical constitution of both substances. This combination forms or results in the formation of a deposit or film on the

antigen surface. The properties of this sensitizing film approximate those of denatured serum globulin.

The specific combination between antigen and antibody may be determined by agglutination or by the resuspension reaction. These reactions are consequent upon the deposit of antibody globulin on the antigen surface. With the progressive formation of a surface deposit, the isoelectric point of the antigen particles approaches that of the deposited substance. This affords further means for demonstrating that specific combination has taken place.

The addition of formaldehyde in sufficient excess to a protein masks the presence of any primary amino groups and leaves the protein with freely titratable carboxyl groups. Such a deaminization should shift the isoelectric point of the protein to the acid side.

This report presents evidence for the existence on the serum-sensitized surface of free primary amino groups which can be substituted without very greatly interfering with the combination of antibody with antigen.

Salmonella pullorum was sensitized with specific antiserum. When sensitization was complete, the sensitized bacteria were divided into two portions. One of these was treated with saline solution, the other with formaldehyde. Agglutination and resuspension reactions were read. The isoelectric points were determined in the microcataphoresis apparatus. The isoelectric point, in the case of maximally sensitized bacteria, was shifted from pH = 5.2 − 5.0 to pH = 4.5 − 4.3. In order to determine whether specific combination would take place if the serum was first deaminized, the specific antisera were treated with formaldehyde. The bacteria were then added (1) suspended in salt solution, and (2) suspended in formalin. Agglutination and resuspension reactions were read. The isoelectric points were determined and found to fall within the range pH = 4.5 − 4.3 in maximal sensitization.

Previous experimental work has shown that most bacteria migrate to the anode when placed in a buffered solution in an electric field. In some cases the bacteria have definite isoelectric points, whereas others retain a negative charge even down to pH values below 2.0. The strain used in the experiments described show only a minimal charge in buffers of any pH studied and this minute charge is not altered by treatment with formaldehyde. With sensitization this organism assumes a definite isoelectric point and this isoelectric point does not vary greatly as sensitization increases.

Thus the shift in the isoelectric point due to treatment of the sensitized bacteria or of the antiserum with formaldehyde does not seem to be due to a removal of antibody globulin film from the antigen but to an alteration in the chemical nature of the film. This alteration is interpreted as an effect upon primary amino groups in the serum-sensitized surface.

Estimations of Cardiac Work During and After an Attack of Angina Pectoris.—Isaac Starr, Jr., Leon H. Collins, Jr., and Francis C. Wood (from the Medical Division of the Hospital of the University of Pennsylvania and the Laboratory of Pharmacology, University of

Pennsylvania). We have been fortunate enough to secure observations on a case of angina pectoris during an attack. Before the attack blood pressure and pulse rate were normal. After the onset of pain, pulse rate and blood pressure increased markedly and respiration was recorded as high. At this time the cardiac output (Starr and Gamble method) was 3.4 liters per min., the cardiac work 6.6 kg. meters per min., the cardiac work per beat 52 gm. meters, the oxygen consumption 200 cc. per min. Twenty minutes later the pain was far less intense, the blood pressure had fallen somewhat, the pulse rate and respiration were also lower. The cardiac output was 2.4 liters per min., the cardiac work 3.6 kg. meters per min., the cardiac work per beat 36 gm. meters, the oxygen consumption 173 cc. After these determinations nitroglycerin was administered and the pain disappeared within 5 minutes. The pulse rate did not change significantly, the systolic blood pressure fell a little but regained its previous level in a few minutes; diastolic pressure and respiration were unchanged. Fifteen minutes after the drug the cardiac output was 2 liters per min., the work 2.5 kg. meters per min., or 28 gm. meters per beat, the oxygen consumption 188 cc.

These data are consistent with the conception that angina is caused by a situation which demands increased cardiac work, for the work decreased as pain diminished. On the other hand they do not seem consistent with the conception that angina is primarily due to coronary spasm, for in this condition one would expect the work of the heart to be diminished during an attack and to increase after it was over.

About two weeks after these observations the patient had an attack diagnosed as coronary occlusion and died. Necropsy was not permitted.

Absorption of Oxygen by the Skin and Its Effect Upon the Vascular Reaction to Stasis and to Histamin.—S. GOLDSCHMIDT and B. MCGLONE (from the Department of Physiology, University of Pennsylvania). The cyanosis, which develops in an arm with the circulation totally or partially occluded, may fail to appear when the part is surrounded by an atmosphere of oxygen. This result is a convincing evidence of the passage of oxygen through the skin into the blood of those vessels which give it color, and is consistent with the findings of previous investigators, notably Shaw and his coworkers,[1] that oxygen may be absorbed by the cutaneous route. The skin of the forearm is usually maintained free of cyanosis under these conditions, while the fingers especially and the hand are quite refractory.

Reactive hyperemia upon release of the occlusion is confined to those parts which were cyanosed or "dusky" before the release. The oxygen, therefore, would seem to prevent the dilatation of the skin vessels which prevails in an arm with arrested circulation, in air or nitrogen.

The failure to obtain a reactive hyperemia under these conditions was examined in the light of the hypothesis of Lewis,[2] which ascribes the control of the small vessels of the skin to an "H" substance, a normal metabolite, the identity of which with histamin Lewis believes to be established by a wealth of convincing evidence.

Our findings, therefore, would seem to indicate that either histamin is not produced or it is destroyed under the prevailing conditions. The idea as developed by Lewis precludes the first possibility, since if one

assumes that dilatation of the small vessels of the skin under a variety of physiologic conditions is due to the "H" substance, one must of necessity, as indeed Lewis does, postulate that the substance is a normal skin constituent, present in but small amounts normally, but piling up when the circulation is arrested.

As to the second possibility, a destruction of the histamin by the high oxygen tension, it might be expected, if this were the explanation of our findings, that there would be a diminution or failure of the histamin reaction when introduced intradermally. On the contrary, the reaction is obtained even in very high dilutions. Indeed, under these conditions one observes a well defined flare, a fact also incompatible with Lewis' belief that this part of the "triple reaction" of histamin is exclusively a reflex arteriolar dilatation.

1. Shaw, L. A., Messer, A. C., and Weiss, Soma: Am. J. of Phys., 1929, **90**, 107.
Shaw, L. A., and Messer, A. C.: Am. J. of Phys., 1930, **95**, 13.
Shaw, L. A., and Messer, A. C.: Am. J. of Phys., 1931, **98**, 93.
2. Lewis, Thomas: The Bloodvessels of the Human Skin and Their Responses, London, 1927.

The Nervous Discharge from the Carotid Sinus.—D. W. BRONK and G. STELLA (from the Johnson Foundation for Medical Physics, University of Pennsylvania). A large body of evidence emphasizes the importance of afferent nerve impulses from the aorta and carotid sinus in the nervous regulation of blood pressure. There is, however, little known regarding the nature of these nerve messages and how they effect this regulation. The present study has therefore been directed to an analysis of the discharge from single pressure receptors in the walls of the carotid sinus in relation to the arterial pulse.

Synchronous with the rapid systolic rise in pressure the end organ discharges impulses at a maximum frequency that may be as high as 120 to 140 a second. If the mean pressure is not high, the frequency rapidly falls during diastole and in many cases there is no discharge of impulses at all during this part of the cycle. The frequency and duration of the discharge is, however, largely dependent upon the form of the pulse curve and the mean pressure.

As the mean blood pressure increases, the average frequency of impulses increases, the duration of the discharge in each heart cycle becomes longer and more end organs come into action. The result of a higher blood pressure is therefore a greater number of afferent impulses going to the centers in the medulla per unit of time. This increased number of impulses presumably acts upon the vasomotor centers in such a way as to cause a decrease in the outflow of sympathetic impulses to the walls of the bloodvessels, with a consequent vasodilatation and fall in pressure.

The Association of Duodenal Ulcer With Adrenal Damage.—CHARLES MCLAUGHLIN (from the Department of Research Surgery, University of Pennsylvania). Observations from 19 dogs with varying degrees of adrenal injury were reported. Ten of these were subjected to bilateral adrenal damage, while 9 had only one adrenal injured. Cauterization

of the adrenal cortex, and to a lesser extent of the medulla, has been undertaken in two stages, using a high frequency coagulating current. A period of from 2 to 3 weeks was permitted to elapse between operations. The average time elapsing between the first operation and autopsy, of the group subjected to bilateral cauterization, was $31\frac{1}{2}$ days. The period before autopsy following the second stage of the procedure varied from 1 to 10 days.

Congestion involving the mucosa of both the stomach and small bowel was noted in 5 cases, being moderate in degree in 3 animals and marked in 2. Congestion of the mucosa of the small intestine alone was much more striking, being present in 10 dogs. Frank gastrointestinal hemorrhage with free blood in the stomach and small intestine was present in 3 dogs. In 15 of the animals definite ulceration was present in the small intestine, being most marked in the duodenum, but present also in the jejunum and upper ileum. In no case was any evidence of gastric ulceration found.

The ulcers were of two distinct types, which we have classified as acute and chronic on the basis of their appearance. In 8 animals the ulceration was of the acute type. The average length of life following the first stage of the operative procedure in this group was 15 days, only 4 of these 9 dogs having been submitted to the second stage operation, so that in 5, only one adrenal was affected.

Seven of the 15 animals presented definite circumscribed ulcers of a chronic type, with heaped up edges and ragged excavated craters. The ulcers appeared in the duodenum, jejunum and upper ileum, from 3 to 8 being found in each animal. No ulcers were ever present above the pyloric ring although in several animals they began just distal to it. There was no evidence of perforation in any case. The average length of life in this group of 5 animals following the first operation was 29 days.

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